

Rimegepant, a CGRP Antagonist, in the
Treatment of Visceral Sensation and Chronic
Abdominal Pain: A Pilot Study

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STUDY PROTOCOL

Rimegepant, a CGRP Antagonist, in the Treatment of Visceral Sensation and Chronic Abdominal Pain: A Pilot Study

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ABSTRACT

Irritable bowel syndrome (IBS) and, particularly, the pain component of IBS lack effective treatments. Antispasmodics, antidepressants and hypnotherapy have all been proposed for the treatment of pain. Their effectiveness in clinical practice is disappointing, despite meta-analyses suggesting efficacy. The study hypotheses are: that rimegepant will be safe, well-tolerated, and will improve abdominal pain in participants with non-constipation IBS. The primary aim is to evaluate the efficacy of rimegepant on abdominal pain scores in participants with non-constipation IBS. Secondary aims of this study are:

#1: To describe the effect of rimegepant on rectal compliance in participants with IBS and chronic abdominal pain.

#2: To evaluate the effects of rimegepant on rectal sensation based on ascending method of limits and on graded rapid phasic distensions in participants with non-constipation IBS and chronic abdominal pain.

#3: To evaluate effects of rimegepant on overall colonic transit in participants with non-constipation IBS and chronic abdominal pain.

#4: To evaluate safety of rimegepant in participants with non-constipation IBS and chronic abdominal pain

Methods: IBS-pain participants will be selected according to the Rome III criteria. Trial participants will continue to receive the same medical therapy throughout the baseline and treatment periods. The study design is a randomized, double-blind placebo-controlled trial of rimegepant at doses and route of administration approved by the FDA for the prophylaxis of migraine headache.

The trial period will consist of a two week run-in period, a 4 week (28-32 days) treatment period, and 4 week post-treatment period. Participants will complete a daily diary regarding abdominal pain and stool consistency. They will also complete questionnaires studies of anxiety and depression and IBS-QOL.

An established and validated method using rectal barostat device will be used to measure rectal compliance and sensation. The standard scintigraphic method to measure colonic transit established in the Clinical Research Trials Unit (CRTU) at Mayo Clinic Rochester will be used to evaluate changes in colonic transit.

Anticipated results and Significance: Rimegepant, at doses and mode of administration approved by FDA for the prophylaxis of migraine headache, will be efficacious in the reduction of abdominal pain and rectal sensation in participants with non-constipation IBS and abdominal pain.

This study will provide an early signal of efficacy that may lead to future randomized, controlled trials.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction that manifests with symptoms of abdominal pain and altered bowel function; the global prevalence in adults, based on Rome III criteria and data from 38 countries comprising 395,385 participants, was 9.2% (95% CI 7.6-10.8).¹ According to these symptom-based criteria, all patients have abdominal pain that is associated with bowel dysfunction, and therefore it is estimated that 9.2% of the population have abdominal pain in association with IBS. IBS with mixed bowel habit (IBS-M) was reported by 33.8% (95% CI 27.8-40.0); 27.8% (24.9–30.7) had IBS-D, 20.0% (16.7–23.4) had IBS-C, and 14.1% (10.0–18.8) had IBS-U (unspecified bowel dysfunction) of people fulfilling criteria for IBS.¹

A characteristic of the abdominal pain is that it is related to the alteration in bowel function such that it is either aggravated during bowel function, or it can be relieved by defecation. It is also accompanied by other symptoms such as abdominal bloating, and distention, and there is sometimes overlap with upper gastrointestinal symptoms including heartburn, fullness after meals, and nausea. Chronic abdominal pain and depression have been associated with IBS.^{2,3}

Antispasmodics, antidepressants and hypnotherapy have all been proposed for the treatment of pain. Their effectiveness in clinical practice is disappointing, despite meta-analyses suggesting efficacy.^{4,5}

CGRP is a widely distributed peptide of the calcitonin family of regulatory peptides with different functions depending on its area of release.^{6,7} Release of CGRP, a neuropeptide, from vesicles in cell bodies, axonal varicosities, and synapses allows a broad diffusion or volume transmission to more distant sites of action than the more locally restricted classical neurotransmitters. CGRP-containing nerve fibers innervate every major organ system of the body, and endogenous CGRP-expressing cells may also be present in those organs. CGRP, an endogenous 37 amino acid peptide contained within pain signaling nociceptive afferents, is abundantly expressed in sensory neurons as well as expressed in nonneuronal cells. Nonneuronal sources of CGRP that have been reported include diffuse neuroendocrine and endocrine cells found in the thyroid (C cells), lung and respiratory tract epithelia, small intestine mucosal endocrine cells, adrenal chromaffin cells, pancreatic islets, and Merkel cells in the skin. CGRP is a member of a gene family of six related peptides: calcitonin, α -CGRP, β -CGRP, amylin, adrenomedullin (AM), and adrenomedullin 2 (AM-2); of these, the two most closely related peptides are α -CGRP and β -CGRP. These two isoforms, α -CGRP (mainly localized in spinal afferents) and β -CGRP (main isoform in the enteric nervous system), regulate numerous physiological pathways, including nociception, vasodilatation, motility, secretion, feeding, olfaction and audition.^{8,9}

Similar to the expression of the CGRP peptide, receptors with CGRP binding sites are broadly expressed in major organ systems of the body. CGRP binding sites consist of a complex of proteins including calcitonin receptor (CTR) or calcitonin-like receptor (CLR) with or without a receptor activity-modifying proteins (RAMPs) which are RAMP1, RAMP2, or RAMP3.¹⁰ The CGRP receptor is comprised of CLR and RAMP1 with α -CGRP and β -CGRP being the most potent ligands.¹⁰ The AMY₁, AMY₂, and AMY₃ receptors are comprised of CTR and RAMP1, RAMP2, or RAMP3, respectively, with α -CGRP, β -CGRP, and amylin being potent ligands.¹⁰ Activation of CGRP and AMY receptors results in downstream signaling of various pathways. The CGRP receptor activation also results in signaling via internalization in endosomes which is linked to persistent activation of nociceptive neurons.¹⁰

CGRP expressing cells and receptors are present through the gastrointestinal system including enteric nervous system, vasculature, muscle layers, mucosa, endocrine cells, and immune cells.⁹ Relative expression of α -CGRP and β -CGRP within the gastrointestinal tract

including the enteric nervous system are illustrated in Figure 1.¹⁰ CGRP and substance P are expressed by visceral afferent fibers originating from dorsal root ganglia (DRG).^{11,12} Up to 90% of spinal afferents innervating the esophagus contain CGRP¹³ and are evenly distributed throughout the whole organ.¹⁴ However, in the rat cervical esophagus, CGRP is not only contained in spinal afferents, but it is also found in vagal afferents innervating the mucosa and submucosa.¹⁵ Within the mouse and rat gastrointestinal tract, CGRP has a major role as a neurotransmitter that regulates motility, secretion, and mucosal homeostasis.^{8,10,11,16,17} Given the major role that CGRP and CGRP receptors play in gastrointestinal function, it is hypothesized that the use of CGRP receptor antagonists may have a role in addressing issues related to irritable bowel syndrome and other GI related disorders. Delafoy et al. showed that CGRP significantly decreased the pain threshold in response to colonic distension in rats.¹⁸ Additionally, the use of a selective CGRP receptor antagonist reversed induced colonic hypersensitivity in nerve growth factor (NGF) and trinitrobenzene sulfonic acid (TNBS) IBS rat models.¹⁸ More recent nonclinical data with an anti-CGRP receptor antibody reversed stress-induced changes in visceral hypersensitivity in a rat model.¹⁹ These nonclinical data support the hypothesis of CGRP involvement in IBS.

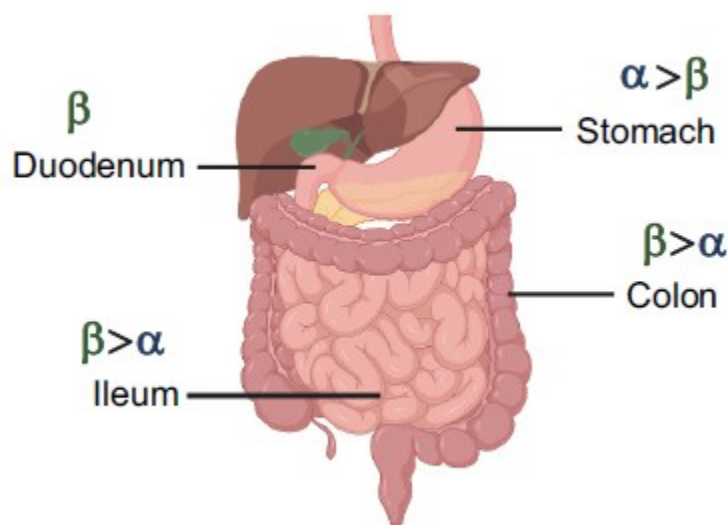


Figure 1. Expression of α -CGRP and β -CGRP within the gastrointestinal tract¹⁰

CGRP receptor antagonists are thought to relieve migraine pain by halting the cascade of CGRP-induced neurogenic inflammation (which leads to peripheral and central sensitization) and inhibiting the central relay of pain signals from trigeminal afferents without vasoconstrictive effects. These mechanisms may be relevant in the context of visceral hyperalgesia in IBS and abdominal pain.

Rimegepant, a Small Molecule CGRP Receptor Antagonist

Rimegepant is an oral CGRP receptor antagonist approved in the USA for acute treatment of migraine with or without aura and preventive treatment of episodic migraine in adults.²⁰ The 75 mg dose of rimegepant was safe and efficacious in multiple, randomized, placebo-controlled clinical trials.²¹⁻²³ A reduction in migraine days per month was recorded with rimegepant 75 mg dosed every other day in a long-term, open-label safety study.²⁴ In a multicentre, phase 2/3, randomized, double-blind, placebo-controlled trial in 695 US adults with at least a 1-year history of migraine, rimegepant taken every other day was effective for preventive treatment of migraine with tolerability similar to that of placebo, and with no unexpected or serious safety issues.²⁵ One precaution necessary is to avoid use in the setting of severe hepatic impairment.²⁶ In

addition, novel anti-migraine treatments including rimegepant were efficacious in prevention of migraine based on a systematic review and meta-analysis (SRMA) and network meta-analysis (NMA).²⁷

Rimegepant is the only CGRP receptor antagonist approved for the acute treatment of migraine, and for the preventive treatment of episodic migraine in adults. Rimegepant is available as an orally disintegrating tablet (ODT), which offers convenience and a potentially faster response time than the conventional tablet formulation. When taken every other day for the preventive treatment of migraine, rimegepant reduced the number and frequency of monthly migraine days, and improved quality of life maintained over the longer term (up to 52 weeks). It was generally well tolerated, with no evidence of hepatotoxicity or cardiovascular toxicity in clinical trials²⁸. Rare cases of Raynaud's phenomenon have been reported in association with its use.²⁹

It is important to note that reports in the FAERS (FDA Adverse Event Reporting System) document GI events with similar frequency across the 3 CGRP-targeting mAbs (eptinezumab, fremanezumab, galcanezumab) for which FAERS data are available, and that nausea and constipation were the GI events most often reported.³⁰ Relatively few adverse events have been recorded through FAERS for the gepants, with nausea (about 10%) and vomiting (about 3%) being the most commonly reported in clinical trials.^{23,31,32} There is evidence that constipation results from the inhibition of calcitonin gene-related peptide's stimulant effect on intestinal peristalsis and secretion, and this is most evident with CGRP-targeting mAbs.³³

Whereas first generation small molecule CGRP receptor antagonists (gepants) demonstrated promising efficacy, their development was discontinued for various reasons, including hepatotoxicity concerns.³⁴ In contrast, second-generation gepants that do not cause hepatotoxicity have been developed and these include rimegepant, which showed extremely low prevalence of any abnormalities of liver enzymes.^{22,23,25}

Migraine, Gastrointestinal Symptoms and Gepants

CGRP plays a role in gastrointestinal nociception, inflammation, gastric acid secretion, and motility. Nausea and vomiting are among the gastrointestinal symptoms associated with migraine, and individuals with migraine may also experience functional upper and lower gastrointestinal comorbidities e.g. GERD, gastroparesis, functional diarrhea or constipation, and IBS. Gastrointestinal symptoms in migraine may be attributable to increased CGRP. Gastrointestinal events in patients with migraine receiving CGRP-based therapies include nausea, vomiting and constipation. GI adverse events with rimegepant recorded through FAERS occurred in 175 of 943 cases, with nausea (106 [11.2%]) and vomiting (27 [2.9%]) being the most common.³⁰ Constipation may also occur as a result of inhibition of effects of CGRP by rimegepant.³⁵ The effects of gepants on gastrointestinal and colonic transit, and on rectal sensation and abdominal pain in participants with non-constipation IBS are unknown.

HYPOTHESIS AND AIMS

The study *hypotheses* are that rimegepant will be safe, well-tolerated, and will improve abdominal pain in participants with non-constipation IBS.

The *primary aim* is to evaluate the efficacy of rimegepant on abdominal pain scores in participants with non-constipation IBS.

Secondary aims of this study are:

- #1: To describe the effect of rimegepant on rectal compliance in participants with non-constipation IBS and chronic abdominal pain.
- #2: To evaluate the effects of rimegepant on rectal sensation based on ascending method of limits and on graded rapid phasic distensions in participants with non-constipation IBS and chronic abdominal pain.
- #3: To evaluate effects of rimegepant on overall colonic transit in participants with non-constipation IBS and chronic abdominal pain.
- #4: To evaluate safety of rimegepant in participants with non-constipation IBS and chronic abdominal pain.

METHODS

STUDY INTERVENTION AND CONCOMITANT THERAPY

Rimegepant

Rimegepant (Nurtec ODT®) is an oral, small molecule, CGRP receptor antagonist approved in the US for the acute treatment of migraine and the preventive treatment of episodic migraine in adults. This is a summary of the pharmacology and dosing of rimegepant in the proposed study:

- Approved Formulation – oral dissolving tablet (ODT)
- Dosing as per Migraine Prevention: 75 mg Every Other Day (EOD) for 4 weeks/28-32 days
- Pharmacokinetics: Tmax: 1.5h; $t_{1/2}$: 11h; bioavailability: 64%
- Drug-drug Interactions: Avoid strong CYP3A4 inducers and strong or moderate CYP3A4 inhibitors
- Hepatic and Renal Impairment: Avoid use in severe hepatic impairment and end stage renal disease
- Notable Adverse Events: nausea (2.7% in rimegepant group vs 0.8% in placebo group); abdominal pain/dyspepsia (2.4% in rimegepant group vs 0.8% in placebo group)

Description of Study Drug

Rimegepant is supplied as a 75 mg white to off-white ODT in a pre-filled blister card containing 8 tablets. The placebo is supplied as a 75 mg white to off-white ODT in a pre-filled blister card containing 8 tablets. Blister cards are to be stored at 15-25°C (59-77°F).

Blinding

Participants will be blinded to their assigned study intervention. Investigators and other site staff will be blinded to participants' assigned study intervention. Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

In order to maintain this blinding, the pharmacy at Mayo Clinic will be responsible for the preparation and dispensing of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense or in visual presentation, following randomization or dispensing. The pharmacy will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study intervention with the investigator.

Study Drug Administration

Rimegepant and the placebo are for oral administration only. Participants will administer 1 ODT every other day (EOD) for 4 weeks (28-32 days). Participant will administer the study

intervention by placing 1 ODT on or under the tongue and allowing to dissolve. Dosing should occur around the same time for each scheduled EOD dose. If a dose of study drug is missed, lost, or otherwise unable to be taken, the participant should note the missed dose and should not take another dose until the next scheduled dosing day.

Dose Modifications

Dose adjustment is not permitted. Dose interruption may be permitted for an adverse effect which is not so severe as to warrant medication discontinuation.

Concomitant Medications

Concomitant medications aimed at relief of visceral pain such as central neuromodulators will only be permitted if the dose has been constant for at least 30 days prior to randomization, and the dose will remain constant throughout the study and 4 week washout period. Strong CYP3A4 inhibitors and strong or moderate CYP3A4 inducers are prohibited while on study treatment (See Appendix 3).

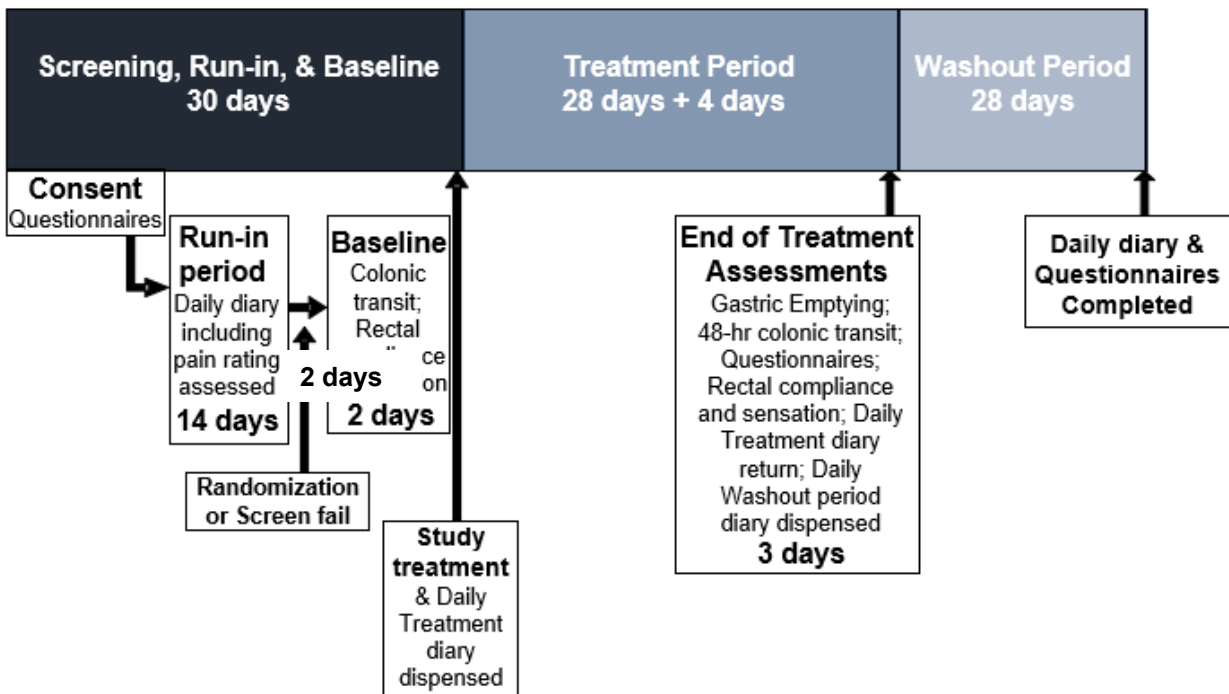
RESCUE Medications: Any additional pain medications other than the medication to which a participant is randomized will need to be justified by the severity of the symptoms and with the approval of the senior clinical investigators (Dr H. Halawi or Dr M. Camilleri).

Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an effective method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4) and will confirm that the participant has been instructed in its consistent and correct use. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

Study Design



Baseline: After recruitment, consent form completion, and screening examination within 30 days of consent, eligible participants (determined after review of the 2-week run in diary) will undergo a colonic transit measurement with scans at 6-8, and 24 hours. After the 24 hr image is obtained, participants will undergo rectal compliance and sensation study. These baseline tests will take up to 2 days.

Clinical Trial: This is a prospective, randomized placebo-controlled trial of rimegepant in participants with non-constipation IBS and chronic abdominal pain where 24 have started their assigned treatment. The randomization schedule will be generated by Pfizer and communicated to the research pharmacy, with the study participants and investigators blinded. Allocation to treatment will be concealed from all participants and investigators. Randomization and delivery of study medication through the clinical research trials unit will occur after the performance of the baseline colonic transit, and rectal sensation and compliance testing. The trial period will consist of a two-week run-in period (before presenting to the clinical research trials unit for the baseline testing), and a 4-week (28-32 days) treatment period. Participants will fill a daily diary regarding abdominal pain, stool consistency and bowel function. They will also complete questionnaires that survey anxiety and depression and IBS-QOL during the screening period and at the end of the 4-week (28-32 days) trial. The final washout phase is a total of 4 weeks, during which the daily diary is continued for 28 days which includes the following questionnaires: Daily Abdominal Pain, Bloating, Flatulence, and Urgency Scores by VAS, Daily Bowel Diary including Bristol Stool Form Scale, and the Likert Scale Questionnaire for Most Intense Pain (0-4) The IBS Quality of Life Questionnaire and Hospital Anxiety Depression Questionnaire will be completed at the end of 4 weeks after the last dose of study medication.

SCHEDULE OF ASSESSMENTS

	Screening	Run-In Period	Baseline	Treatment Period	End of Treatment	Washout Period	Notes
Study Days	-30 to -1	-18 to -5	-3 to 0	1 to 28	28	29-56	
Window	0	±3 days	±1 day	+4 days	+ 4 days	+4 days	
Informed consent	X						Prior to any study procedures
Inclusion/exclusion criteria	X		X				
Demographic information and medical history	X						
Prior and concomitant medication	X	X	X	X	X		
Physical Exam	X				X		Exam may be delayed if remote consenting
Randomization		X					After completion of screening assessments
Rectal Compliance and Sensation study			X		X		
Pregnancy test if required	X		X		X		Prior to baseline assessments and radioisotopes
Gastric and colonic transit study			X		X		
Talley Bowel Questionnaire	X						
Daily Abdominal Pain Score by VAS	X	X	X	X	X	X	
Daily Bowel Diary including Bristol Stool Form Scale	X	X	X	X	X	X	
IBS Quality of Life Questionnaire	X				X	X	
Hospital Anxiety Depression Questionnaire	X				X	X	
Adverse Events				X	X	X	Recorded from study day 1 through washout period
Study drug administration				X	X		Administered every other day through the end of treatment assessments
Dispense study drug			X				

STUDY PARTICIPANTS

Twenty-four participants with non-constipation IBS and chronic abdominal pain will be recruited for enrollment. Participants will meet specific Rome III IBS diagnostic criteria.

The rationale for NOT using Rome IV criteria stems from the evidence in the literature that documented that the Rome IV criteria actually select participants with higher psychological or psychiatric burden and higher pain severity that may be more appropriate for a central neuromodulator or antidepressant approach. This experience has been documented in studies from Europe, North America and China.³⁶⁻⁴⁰

All participants will be evaluated by a clinical rater using the Hospital Anxiety and Depression *HADS) at screening (which will be used as the baseline assessment if potential participant passes screening phase and is eligible for participation), the end of treatment and 4 weeks after last dose. This is a satisfactory and validated alternative to other questionnaires such as the Beck Depression Inventory.⁴¹ Functioning will be evaluated with IBS quality of life questionnaire at the beginning, end of the study treatment, and 4 weeks after last dose. Participants will be evaluated with the daily bowel diary and pain, bloating, flatulence and urgency VAS and most intense pain ratings for 4 weeks after completing medication treatment. Potential participants with high anxiety or depression scores will be referred to their local internist for further management.

The participants' work-up will include a medical history and physical exam. The review of systems will include assessment of abdominal symptoms (pain and altered bowel function), sensory symptoms in upper and lower limbs and history of headache. Physical examination will include vital signs (T, P, R, BP, level of pain on 0-10 scale), examination of the heart and abdominal examination.

All medications used by study participants, and the number/frequency of assigned medication taken will be recorded. Participants will be on stable doses of any central neuromodulators for at least 30 days prior to enrollment and these medications will be maintained at the same dose and frequency throughout the study including the 28 day follow up. Changes in psychiatric or non-opioid pain medications will be permitted only if clinically indicated as RESCUE medications.

In this study, we wish to address pain in participants with visceral hypersensitivity rather than those with severe affective disorder.

At screening, all participants will complete questionnaires regarding bowel function, anxiety and depression and quality of life.

Run-in period: Two weeks prior to randomization a daily diary including pain will be provided for assessment of pain intensity. Abdominal pain intensity will be assessed by using a daily abdominal pain score by VAS that asks participants daily to rate their average abdominal pain over the past 24 hours. A score of ≥ 30 on the 100 mm VAS averaged over 7 consecutive days of the 2 week run-in period will be meaningful and adequate for randomization. In addition, stool form, frequency and ease of passage will be collected using the daily stool diary questionnaire. Bloating, flatulence, urgency, and most intense pain will also be collected.

Inclusion criteria:

1. Participants will be 18-70 years of age;
2. Participants will have non-constipation IBS [that is IBS-D (diarrhea), IBS-M (mixed), or IBS-U (unspecified)] with chronic abdominal pain diagnosed or documented in their medical records at Mayo Clinic with chronic pain documented for ≥ 3 months;
3. Participants will have subjective pain ratings of ≥ 30 on the 100 mm VAS during at least 7 consecutive days of the 2 week run-in period for enrollment; criterion required by FDA for recruitment of patients in therapeutic trials in IBS-pain;
4. Participants will be capable of providing informed consent.

Exclusion criteria:

1. Diagnosis of moderate-severe depression as per HADS ≥ 15 ;
2. Alcohol or illicit substance dependence or abuse in the past 12 months;
3. Dementia, unprovoked seizure history, seizure disorder;
4. Pregnancy (all women of childbearing potential will be required to have a negative pregnancy test prior to initiation, and will be on a highly effective method of contraception, as detailed in the consent form);
5. Significant change or increase in antidepressant or pain medications within the last four weeks; significant change in primary treatment interventions for pain in the past four weeks;
6. Medically unstable;
7. Severe hepatic or renal impairment, such as baseline AST or ALT >2.5 X upper normal limit or end-stage renal disease with estimated glomerular filtration rate or creatinine clearance <15 mL/min. Although Rimegepant is rarely associated with abnormal circulating liver enzymes, we shall exclude patients with baseline AST or ALT greater than 2.5 times the upper limit of normal;
8. Concomitant use of strong CYP3A4 inhibitors and strong or moderate CYP3A4 inducers;
9. Participants who report nausea several times per week or daily on the baseline bowel disease questionnaire (question # 16) will be excluded from the study because of the low risk of nausea induced by the treatment which was estimated at approximately 3% for rimegepant compared to 1% for placebo.

Questionnaires, Clinical Evaluation and Data Collection

Questionnaire based data will be collected using validated questionnaires: (see appendix)

- Abridged Talley Bowel Disease Questionnaire⁴² for screening
- Talley Bowel Disease Questionnaire⁴²
- IBS Quality of Life Questionnaire⁴⁵
- Hospital Anxiety Depression Questionnaire⁴⁶
- Daily Likert Scale Questionnaire for Most Intense Pain (0-4)⁴³
- Daily Abdominal Pain Score by Visual Analog Pain Scale (VAS)
- Daily Abdominal Bloating Score by Visual Analog Pain Scale (VAS)
- Daily Abdominal Flatulence Score by Visual Analog Pain Scale (VAS)
- Daily Abdominal Urgency Score by Visual Analog Pain Scale (VAS)
- Daily Bowel Diary including Bristol Stool Form Scale⁴⁴

Participants must meet the inclusion and exclusion criteria previously described, and they will be evaluated by a study co-investigator prior to enrollment. Potential participants will then be invited for the screening examination.

Discontinuation of Study Intervention and Participant Withdrawal from Study

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- Clinically significant safety reasons as judged by the investigator;
- Severe non-compliance to the protocol as judged by the investigator;
- Pregnancy;
- Development of a condition or acute event that necessitates treatment with one or more prohibited medications;
- Withdrawal of informed consent.

METHODS FOR PHYSIOLOGICAL ENDPOINTS

The standard scintigraphic method to measure colonic transit established in the Clinical Research Trials Unit (CRTU) at Mayo Clinic Rochester will be used to evaluate changes in colonic transit.⁴⁷⁻⁵⁰

Colonic transit

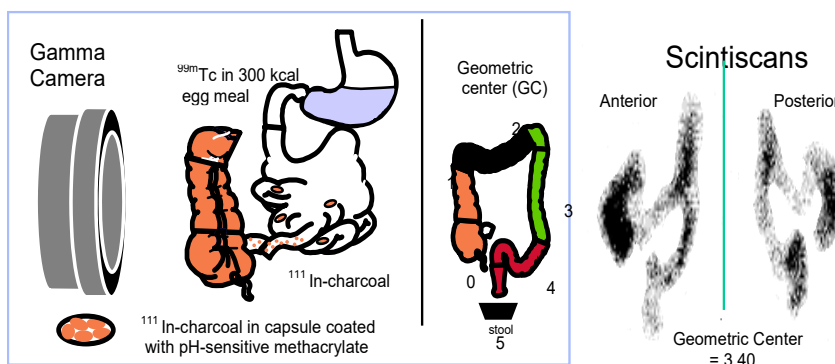
A validated scintigraphic method to measure gastric, small bowel, and colonic transit is shown.

Figure: Scintigraphic method to measure whole gut transit.

Note the methacrylate-coated capsule dissolves in the alkaline pH of the distal ileum to release ¹¹¹In-labeled activated charcoal particles to evaluate colonic transit on sequential scans.⁴⁷ In this study we propose to measure only colonic transit in the participants with non-constipation IBS.

Colonic geometric center (GC, weighted average of isotopic counts) in colon at 4, 24 and 48 hours provide excellent summaries of colonic transit with similar diagnostic accuracy as more detailed, costly, and time-consuming analyses.^{48,49}

Data obtained in patients with IBS are summarized from a study of almost 300 patients.⁵⁰



$$(\%AC \times 1 + \%TC \times 2 + \%DC \times 3 + \%RS \times 4 + \%stool \times 5) = GC$$

	IBS-C/FC	IBS-D/FD	IBS-M	Healthy Controls
Colonic GC 24**	2.0 ± 0.1	3.2 ± 0.1	2.3 ± 0.1	2.4 ± 0.1
(n=453)	(n=118)	(n=138)	(n=30)	(n=167)
Colonic GC 48**	3.0 ± 0.1	4.3 ± 0.1	3.9 ± 0.2	3.6 ± 0.1
(n=411)	(n=118)	(n=112)	(n=30)	(n=151)

Rectal Compliance and Sensation by Barostat

An established and validated method using rectal barostat device will be used to measure rectal compliance and sensation.⁵¹

After completing the 48 hour scan that completes the colonic transit measurement, all study participants will undergo the rectal compliance and sensation test. A rectal catheter with a polyethylene bag attached (length 22 cm; capacity 600 ml) will be inserted into the rectum so that the middle of the balloon is located approximately 10 cm from the anal verge. After a 5 minute recovery period, the catheter will be connected to a barostat (G&J Electronics Inc., Toronto, Ontario, Canada) and the bag will be unfolded by inflation with 75 ml of air, followed by complete deflation. After a 10 minute recovery period, to decrease the effects of abdominal viscera on the balloon volume, the participants will be placed in a semi-prone position and the foot end of the bed elevated 15 degrees. An initial "conditioning" distension of the rectum will then be performed in which the pressure is increased from 0 mmHg in steps of 4 mmHg for 15 seconds per step until 20 mmHg was reached. This "conditioning" distension to 20 mmHg renders subsequent assessments of compliance and perception more reproducible.⁵¹ The bag is then deflated to 0 mmHg and the participants are allowed to rest for 10 minutes before proceeding to the ascending method of limits. During this rest, the VAS of "tiredness", "peace", "worried", and "activity" scores will be collected.

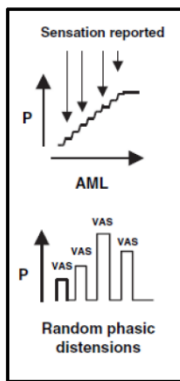


Figure shows experimental procedure for measurement of rectal compliance by ascending method of limits (AML), sensation thresholds (indicated by arrows) and sensation ratings by random order pressure distensions and recording symptoms using 100mm visual analog scales

Ascending method of limits: compliance and sensory thresholds

Rectal sensory thresholds and compliance are measured by ramp inflation, increasing in steps of 4 mm Hg for 1 minute per step from 0 to a maximum 60 mm Hg. Thresholds for gas, first desire to defecate, urgency, and pain are indicated by the study participants by pressing a button at the distension pressure at which sensations are perceived. Ramp inflation is

terminated as soon as participants reported the first sensation of pain.

The bag is deflated and BOP is determined by pressure in the bag increased from 4 mm Hg in steps of 2 mm Hg for 1 minute per step until respiratory excursions are observed. The baseline operating pressure (BOP) set 2 mm Hg above the minimal distension pressure at which respiratory excursions are clearly recorded from the barostat tracing. Once BOP is determined there is another rest for 10 minutes.

Random order phasic distensions: sensory ratings

Phasic distensions of 12, 24, 30 and 36 mm Hg above BOP are each applied once in random order, (the order being provided before the start of the study by the biostatistician), with the participants blinded to the distension order. Each distention is maintained for 60 seconds with an interval between distensions of 2 minutes with the balloon deflated to BOP. Distension pressure is associated with intensity ratings that are generally proportional to the magnitude of the distension pressures.⁵²⁻⁵⁴ Participants mark three separate 100 mm visual analog scales (VAS) 30 seconds after the onset of the distension for the sensations of gas, urgency, and pain. These scales are anchored at each end by the descriptions 'unnoticeable' and 'unbearable'. Pressure is immediately released if the participant reported greater than 80 mm of pain on the VAS scale and higher distensions are not subsequently administered. During the assessment of sensation, the interaction between the participant and the study investigator is kept to a

minimum. Participants will also complete another VAS questionnaire to describe their sense of tiredness, peace, worry and activity before the first measurement of sensation.

Data analysis for compliance and sensory endpoints

The following measurements are derived: (i) the sensory thresholds for gas, first desire to defecate, urgency, and pain during ascending method of limits, (ii) the sensation score (gas, urgency, and pain) in response to the four phasic distensions (12, 24, 30 and 36 mmHg above BOP), and (iii) rectal compliance.

The sequential proportionate volumes (observed volume/maximum observed volume) will be used to obtain a pressure corresponding to half the maximum observed volume using a computer-based linear interpolation algorithm.⁵⁵ Thus, the summary value for each compliance curve will be calculated from the pressures corresponding to the volumes just above and just below the half maximum volume. This provides the specific pressure ($Pr\ 1/2$) corresponding to one half of the maximum observed volume, for each participant, where a smaller $Pr\ 1/2$ corresponds to higher rectal compliance.

STATISTICAL ANALYSIS

A. *Clinical Data*

- a. **Abdominal pain score:** the average pain score each day, as measured by the 100 mm VAS, over the treatment period will be calculated and compared between groups using an unpaired analysis (t test or rank sum test if not normally distributed). The averages during run-in 2-week period will be available to conduct analysis using the baseline measurement as covariates.
- b. **Clinical scales for depression, quality of life** (HADS and IBS-QOL). These summaries will be obtained from measurements made at baseline, at the end of treatment, and 4 weeks after treatment ends.

In addition to calculating these summaries, demographic and other information, including participant age and gender, as well as other medications will be recorded for each participant and summarized as appropriate for the type of data.

Treatment success for chronic pain is defined as a 30% decline in subjective pain ratings on visual analog scales for the treatment group compared to the placebo treatment group. An “Intent to Treat” data analysis will be used given the possibility that some participants will not be able to complete the study. Descriptive statistical analysis and unpaired t-tests (or rank sum test) will be used.

B. *Physiological Data*

Colonic Transit

The covariates to be considered for inclusion in the ANCOVA models for colonic transit are gender, BMI, HAD scores (anxiety and depression scales), the BDQ Somatic Symptom Checklist (SSC) score. These will be considered for inclusion by checking plots of residuals (from the ANCOVA models) against these scores. The analysis will compare colonic transit between the two treatment groups.

Gastric Emptying

Given the reports of nausea and vomiting in participants with migraine as well as observations of these symptoms during clinical trials of CGRP receptor antagonists, we will also measure gastric emptying $T_{1/2}$ (minutes) and proportion emptied at 4h (%) at the end of 4 weeks treatment and compare the results for the active treatment group to those of the placebo group. Sex and BMI will be considered as co variates in this analysis.

Sensory Ratings

The assessment of phenotype associations with observed sensory ratings (rectal sensation VAS scores) will be based on analysis of covariance (ANCOVA) for repeated measures (the four phasic distension levels). Each type of VAS score will be analyzed individually (first sensation, gas, urgency, and pain). The covariates to be included in the ANCOVA models for each VAS score were age, sex, BMI, the “tiredness”, “peace”, “worried”, and “activity” VAS scores, the HAD scores, and the BDQ SSC score. Though most of these scores may not be significant covariates in these models, due to the nature of the responses, it is appropriate to include them. In addition, the corresponding pressure (12, 24, 30, 36 mmHg) at each phasic distension level (the repeated factor) is included in each of these ANCOVA models along with the main effect term for phenotype (e.g. age, sex, BMI), and the 2-way interaction term for phenotype by pressure.

Sensation pressure thresholds

A “time to event” approach (i.e. pressure required to evoke specific sensations) will be used to assess four sensation thresholds (first desire to defecate, gas, urgency, and pain). Since some threshold levels are “censored” (e.g. pain not evoked by the maximum distension pressure used according to the protocol approved by the IRB), a Kaplan-Meier summary of the pressure thresholds will be used to univariately depict the cumulative probability of evoking the sensation, and proportional hazards regression models will be used to assess group effects separately for each of the sensation types. The same covariates listed above used in the analyses of sensation VAS ratings will be included in the proportional hazards regression models, in particular the ratings of “tiredness”, “peace”, “worried”, and “activity” recorded during the sensation studies.

Rectal compliance

The covariates included in the ANCOVA models for fasting colonic tone and compliance $Pr \frac{1}{2}$ values will be age, gender, BMI, the “tiredness”, “peace”, “worried”, and “activity” scores, the HAD scores, and the BDQ somatic symptom score.

Endpoints

Primary Endpoint

is abdominal pain scores in participants with non-constipation IBS

Summary of Secondary Endpoints will be focused on characterizing rectal compliance and sensation, and colonic transit,

The *secondary endpoints* for analysis will be:

- a. Colonic transit geometric center at 24 hours
- b. Colonic transit geometric center at 48 hours
- c. Gastric emptying of solids $T_{1/2}$ (minutes) and % emptied at 4h
- d. Rectal compliance
- e. Rectal sensation during ascending method of limits
- f. Rectal sensation during random order, graded phasic distensions
- g. IBS-QOL
- h. Safety/adverse effects

Sample Size

This study is meant to be a pilot study that will provide preliminary information regarding the usefulness of treating participants chronic abdominal pain associated with non-constipation IBS with rimegepant.

The estimated effect size (with $n=12$ per treatment group) for each of the primary and secondary endpoints is based on power calculation using data acquired from patients with IBS-D at Mayo Clinic^{56, 57}.

Table 4. Key Gastrointestinal Physiologic Data in 163 People Based on Bowel Function Subgroup

	Healthy controls	IBS-C	IBS-D	IBS-M
Number of males	41 (0)	49 (0)	44 (3)	29 (0)
Fasting gastric volume, mL	226 ± 11	229 ± 11	247 ± 11	222 ± 12
Postprandial gastric volume, mL	736 ± 13	740 ± 14	735 ± 14	770 ± 17
Δ postprandial fasting gastric volume, mL	511 ± 13	525 ± 12	488 ± 12	548 ± 19 ^a
Proportion of GE at 2 h	0.47 ± 0.02	0.49 ± 0.02	0.45 ± 0.02	0.42 ± 0.03
GE, T1/2, min	126.0 ± 4.4	126.8 ± 4.7	135.5 ± 5.6	137.6 ± 6.0
Satiation: maximum tolerated volume, mL	1028 ± 44	1044 ± 40	1046 ± 45	1106 ± 81
Satiation: aggregate symptom score	158 ± 14	186 ± 10	188 ± 12	184 ± 16
Colonic filling at 6 h, %	48 ± 5	54 ± 4	56 ± 3	44 ± 5
Colon transit GC 24 ^b	2.35 ± 0.16	2.03 ± 0.10	3.03 ± 0.19	2.34 ± 0.10
Colon transit GC 48 ^c	3.23 ± 0.18	3.0 ± 0.13	4.14 ± 0.17	3.94 ± 0.16
Rectal compliance, Pr _{1/2} , mm Hg	12.6 ± 0.8	12.5 ± 0.8	14.2 ± 0.6	14.0 ± 0.9
Threshold for first sensation, mm Hg	7.8 ± 0.5	7.8 ± 0.7	8.4 ± 0.7	8.1 ± 0.8
Threshold for gas, mm Hg	13.8 ± 1.5	14.0 ± 1.2	13.3 ± 1.2	14.5 ± 1.6
Threshold for pain, mm Hg	29.1 ± 2.1	29.0 ± 2.0	31.0 ± 1.8	31.0 ± 2.2
Threshold for urgency, mm Hg	17.5 ± 1.1	20.5 ± 1.6	18.8 ± 1.4	17.4 ± 1.2
Sensation rating, pain 30 mm Hg	55.1 ± 4.5	52.5 ± 4.6	55.3 ± 4.2	54.3 ± 5.6
Sensation rating, urgency 30 mm Hg	74.9 ± 2.8	71.5 ± 3.3	74.4 ± 2.5	74.3 ± 3.1

NOTE. There were 41 controls and 122 patients with IBS (data are mean ± SEM). For the number of participants undergoing each measurement, see the Methods section.

^aP = .017 versus healthy controls.

^bOverall P < .001.

^cOverall P < .001.

In a prior study that evaluated abdominal pain scores on a daily diary 0-100 mm for severity of abdominal pain, patients with IBS had the following pain severity at baseline prior to treatment (Pain, 100-mm VAS 37.2 (27.1–49.5) (57)

parameter	Mean	SD	Effect size (absolute and % of mean), 80% power; α=0.05
Average pain score on 0-100mm VAS	37.2	11	13.16 (35%)
Colonic transit GC24	3.03	1.25	1.5 (50%)
Colonic transit GC48	4.14	1.12	1.34 (32%)
Rectal compliance	14.2	3.94	4.7 (33%)
Threshold for first sensation	8.4	4.59	5.5 (65%)
Threshold for gas	13.3	7.87	9.4 (71%)
Threshold for pain	31	11.81	13.3 (43%)
Threshold for urgency	18.8	9.18	11 (59%)
Sensation rating pain 30 mmHg	55.3	27.55	33 (60%)
Sensation rating urgency 30mm Hg	74.4	16.4	19.6 (26%)
Gastric emptying T1/2	135.5	36.7	44 (32.6%)
Proportion of gastric emptying at 4h	0.45	0.13	0.156 (34.7%)

FEASIBILITY AND TIME FRAME

Many patients with chronic pain associated with non-constipation IBS have been identified by clinicians in the Division of Gastroenterology and Hepatology at Mayo Clinic (Rochester). It is quite feasible that 24 participants can start their assigned treatment in this study and all physiological and patient response endpoints (each over 11 weeks [2-3 week baseline, 4 weeks (28-32 days) on treatment, 4 weeks washout]) completed in one year. In a recent 4 year NIH-funded study, we included 205 patients with non-constipation IBS and these were selected after screening 1744 primary or secondary referral patients with IBS-D.⁵⁸

Strengths

This is the first study examining the use of rimegepant in participants with chronic, often treatment-resistant abdominal pain associated with non-constipation IBS. As these individuals often have treatment-resistant pain, any useful new treatment options would be of significant benefit.

Limitations

- a. Small sample size
- b. Generalizability

POTENTIAL RISKS

Rimegepant is an FDA-approved drug with a well described safety profile with a low frequency of moderate adverse events such as gastrointestinal AEs, that is constipation and nausea; it will be administered as approved in migraine prophylaxis by FDA for a period of 4 weeks. Because of the potential for anti-CGRP medications to inhibit colonic motility, patients with constipation in association with IBS will be excluded from the current study.

There is not enough medical information to know what the risks might be to a breast-fed infant or to an unborn child in a woman who takes part in this study. One of the following birth control measures must be used by all women who can become pregnant and are sexually active (or their sexual partners) while in this study: oral contraceptive or barrier method, preferably with use of a spermicidal foam/gel. Women who can still become pregnant must have a pregnancy test before taking part in this study. Women with a positive pregnancy test will be ineligible for enrollment.

Rectal Intubation and Measurements

There is a small risk of damage to the rectal mucosa by placement of the rectal tube and barostat balloon. This risk is small given the fact that patients with irritable bowel syndrome do not have any rectal mucosal inflammation, and the study is conducted by a research team with considerable experience with performing such studies of rectal compliance and sensation.

Radiation exposure in this study involves radiation exposure from the ¹¹¹In used to measure colonic transit. These exposures conform to previously approved levels of radiation exposure approved by the Radiation Control Committee at Mayo Clinic. The radiation dosimetry and organ exposures (in mrad) are listed below.

GASTROINTESTINAL AND COLONIC TRANSIT TESTS

Radiopharmaceutical	Act mCi	Body	Gonads	Breast	Red marrow	Lung	Thyroid	Bone	ULI	Colon	Stom	Blad	Liv	Esoph	Other
											-ach	-der	-er	-agus	
¹¹¹ In charcoal	0.10	20	140		20				380	740	60	40	10	160	
^{99m} Tc-sulfur colloid	1.0	20	90		20				420	300	130	20	10	220	

(mrad= unit of radiation absorbed dose to organs)

H_e or the radiation effective dose to the body summarizes the risk to the whole body as the individual doses to each of the organs; effective dose is used to compare risks among various types of x ray and radionuclide studies: ¹¹¹In Cl₃ 0.1 mCi : H_e 142 mrem (where mrem= radiation equivalent dose); ^{99m}Tc sulfur colloid 1.0 mCi, H_e = 90 mrem; note that participants will receive ¹¹¹In on 2 occasions separated by about 1 month

In view of the radiation exposure, all females of childbearing age will be required to have a negative urine pregnancy test within 48 hours of performance of fluoroscopy or the radioisotope studies.

Significance of the Proposal

Rimegepant, at doses and mode of administration approved by FDA for the prophylaxis of migraine headache, will be efficacious in the reduction of abdominal pain and rectal sensation in participants with non-constipation IBS and abdominal pain.

This study will provide preliminary data to support the calculation of the variance in response and therefore plan a future controlled trial.

Gender/Minority Mix

All efforts will be made to recruit participants of both genders, and of diverse ethnicity.

HUMAN STUDIES PROTECTION

I. CONFIDENTIALITY

Mayo Clinic upholds the most stringent standards for protection of human subjects and privacy while balancing the crucial importance of data sharing to advance medical science. This is applied to all patients participating in research activities, direct care and as study participants. Protection of privacy is assured based on Mayo Clinic's standards and procedures, including rules in full compliance with current HIPAA regulations. All staff members are trained in privacy compliance and held to the strictest standards.

Mayo Clinic requires that formal approval be obtained from all appropriate committees before medical records are reviewed or patient contact is initiated.

A. Protection of Subject Privacy - During this study, medical history and physical examinations will be performed, and questionnaires will be administered. Additional research material will be: review of medical records (of those who authorize review of the records for research purposes), and prospectively acquired measurements of gastrointestinal motility, rectal sensation, and rectal compliance. All data including those from the biological samples will be used exclusively for research purposes.

Data will be kept in strict confidence. No information will be given to anyone without permission from the participant. This statement guarantees confidentiality. Confidentiality is assured by use of identification codes. All data, whether generated in the laboratory or at the bedside, will be identified with a randomly generated identification code unique to the subject.

ONLY at the request of the participant, clinically-relevant measurements based on clinically-approved tests including gastrointestinal and colonic transit, gastric accommodation, esophageal and anorectal manometry **will be made available to the patient and at their request to their neurologist or other physician involved in their clinical care.**

B. Database Protection - The database is secured with password protection. DNA samples that are analyzed in future, or stored, will be linked in a de-identified manner using a study identification code (rather than any identifiable information) to the other data acquired in the study.

Confidentiality during AE reporting - Adverse event reports and annual summaries will not include subject-identifiable material. Each will include the identification code only.

C. Data Sharing -

Results of the study will be shared with subject participants.

D. Identifiers - In general, clinical data used for research is de-identified, whereby all information that could link to an individual patient's identity is removed. Patient information is coded and coding information secured. Individual participants are identified in computer files only by a unique study number which bears no relationship to personal identifiers. Healthcare information is utilized by staff solely on a "need to know" basis.

E. Confidentiality - Dissemination of healthcare and insurance information is entirely compliant with current healthcare information legislation. In the case of clinical information in research, all participants are required by Minnesota law to be informed of use of their information in research projects and have the right to decline participation. In addition, informed consent policies are rigorously employed and monitored. Every member of the Mayo Clinic staff, both clinical and research, must take training annually in patient information security to be fully compliant with federal HIPAA regulations.

F. Disposition of Data - Along with the requirements of state privacy laws and more recently HIPAA, strict institutional procedures have been put in place to help maintain patient (subject) privacy. All study records are kept in a password-protected electronic study folder. Individual participants are identified in associated computer files and analyzed only by a unique study number, which bears no relationship to personal identifiers. Only de-identified data will be entered into the electronic data record. Only the authorized personnel from the study team will have access to this data.

G. Data Security - Mayo Clinic Rochester has a complete electronic medical record. With our long-standing commitment to privacy, extensive measures have been instituted to insure security of the clinical database. The mainframe computers and local area network (LAN) are entirely behind an extensive information firewall that is routinely maintained and upgraded. Staff access electronic data only on a "need to know" basis. Staff access and use of this electronic medical record data is monitored by the Information Management and Technology Committee. Clinical research data are de-identified with respect to patient's origin, and data management is held to the same standards as clinical healthcare information. Hard copy data of patient information for research is maintained in locked and secure cabinetry within the office of the study coordinator. Access to this building is carefully controlled by Mayo Clinic security personnel and requires keycard access.

Managing data security is mandatory. Before accessing secured applications and data through the internet or intranet, each user will be required to login using their assigned user ID (LAN ID) and password (which has to be updated every 6 months). Group files will be maintained to control access to directories, applications, and data. The user ID must be a member of the group file in order to access the group's data or application. The groups are assigned roles to the data and applications (e.g., viewing authority to a protocol document, adding and updating patient data, etc.). To get to specific secured directories, applications, and data, the user ID and password are verified at a folder and application level; thus, members are restricted to viewing only applications and data that pertain to their role. Applications will also be run on secure socket layers.

H. Institutional Review Board Approval and Other Reviews - The Mayo Clinic Institutional Review Board will review the proposal's DSMP when the study protocol will be submitted after funding decision. Usually, the IRB refers the investigators to the Mayo Clinic Legal Contract Administration to review the data use agreement.

The study will be submitted and receive approval by the Gastroenterology and Hepatology Division Research Committee prior to submission to the IRB.

ADVERSE EVENT INFORMATION

Definition - An adverse event (AE) is any untoward medical occurrence in a subject temporally associated with participation in the clinical study. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Each patient must be evaluated for the development of any adverse events. This information will be obtained in the form of non-leading questions (e.g., "How are you feeling?"), from signs and symptoms detected during each examination, from laboratory evaluation, by observations of study personnel, and by spontaneous reports from participants.

Monitoring of adverse events will be conducted throughout the study starting after receiving the first dose of medication. Adverse events will be recorded in the CRFs. Serious adverse events will be recorded through 28 calendar days after the last administration of study treatment. All adverse events shall be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

A **serious adverse event (SAE)** is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event - Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Inpatient hospitalization or prolongation of existing hospitalization - Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry, are not considered adverse events if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned).
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important medical event based upon appropriate medical judgment - An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but may be considered a serious adverse event when, based upon appropriate medical judgment, it may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for serious adverse events.

Procedures for Adverse Event and Serious Adverse Event Reporting

Each participant will be carefully monitored for the development of any adverse events. All adverse events (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate page of the CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an adverse event and must be recorded on the appropriate pages of the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Unexpected, serious, and/or intervention-related SAEs will be reported to the independent monitor, IRB, CRTU, and Pfizer within 24 hours of the institutional awareness or immediately if fatal or life-threatening.

Anticipated or unrelated SAEs will be reported to the independent monitor (as in the DSMP), IRB, CRTU, and Pfizer within 24 hours of the institutional awareness. In the annual SAE summary, the independent monitor shall state that he has reviewed all adverse reports.

The investigator will promptly notify the IRB of all unexpected serious adverse drug reactions involving risk to human subjects. An unexpected event is one that is not reported in the Physicians' Desk Reference manual regarding the study drugs.

Exposure during pregnancy and lactation are reported independently from any associated SAE. Medication errors and overdoses are reportable only if associated with an SAE.

Occupational/environmental exposure is reported independently from any associated AE/SAE. Lack of Efficacy is reportable only if associated with an SAE.

Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are reportable SAEs. If a Study subject develops abnormal values in aspartate transaminase ("AST") or alanine transaminase ("ALT") or both, concurrent with abnormal elevations in total bilirubin and there is no other known cause of liver injury, that event would be classified as a Hy's Law Case.

For both serious and non-serious adverse events, the investigator will determine both the intensity of the event and the relationship of the event to study drug administration.

The **intensity of all adverse events**, including clinically significant treatment-emergent laboratory abnormalities, and potential systemic reactions, will be graded according to the National Cancer Institute **Common Terminology Criteria for Adverse Events** (CTCAE) Version 5.0. The CTCAE grade refers to the severity of the adverse event and ranges from Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) and Grade 4 (life-threatening or disabling) to Grade 5 (death related to adverse event).

Adverse events not listed in the CTCAE (e.g., physical signs or symptoms) will be classified as follows:

- **Mild:** discomfort noticed; no disruption of normal daily activity; no major impact on patient
- **Moderate:** discomfort sufficient to reduce or affect daily activity; causes minor inconvenience
- **Severe:** inability to work or perform normal daily activity; causes a substantial disruption to the patient's wellbeing
- **Life threatening:** represents an immediate threat to life

Relationship of Adverse Events to Study Procedure

<input type="checkbox"/>	The PI will determine the relationship of AEs to the test procedure/device/agent as definitely related, probably related, possibly related, unrelated, or unknown.
<input checked="" type="checkbox"/>	<p>The PI will use an alternative attribution scale (specify):</p> <ul style="list-style-type: none"> • None: No relationship between the event and the study procedure. The event is related to other etiologies, such as concomitant medications or subject's clinical state. • Unlikely: The current state of knowledge indicates that a relationship to study procedure is unlikely or the temporal relationship would not have had any reasonable association with the observed event. • Possible: A reaction that follows a plausible temporal sequence from the study procedure and follows a known response pattern to the procedure. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject. • Probable: A reaction that follows a plausible temporal sequence from the study procedure and follows a known response pattern to the procedure and cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

For the purpose of safety analyses, all adverse events that are classified as possible or probable will be considered treatment-related events.

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APPENDIX 1: Standard, Validated Questionnaires

Bristol Stool Scale

Consistency of Stool:

Stool form	Appearance	Type
Separate hard lumps, like nuts (hard to pass). Result of slow transit		1
Sausage-shaped but lumpy		2
Like a sausage but with cracks on its surface		3
Like a sausage or snake – smooth and soft		4
Soft blobs with clear cut edges (easy to pass)		5
Fluffy pieces with ragged edges, a mushy stool		6
Watery, no solid pieces. Result of very fast transit		7

Ease of Passage:

1. Manual de-impaction required
2. Enema or suppository required to initiate bowel movement
3. Some straining necessary to pass bowel movement
4. Easy normal passage of stool without straining
5. Urgent need to pass bowel movement spontaneously; **no** abdominal pain or discomfort present
6. Urgent need to pass bowel movement spontaneously; abdominal pain or cramping present
7. Incontinent of bowel movements

<div style="display: flex; justify-content: space-between; align-items: center;"> <div> <h2 style="margin: 0;">Daily Diary</h2> <p style="margin: 0;">Date: </p> </div> <div style="text-align: right;"> <p style="margin: 0;">If you had no bowel movements today, please check this box: <input type="checkbox"/> no bowel movements today.</p> <p style="margin: 0;">Please record the time you took the study medication today: _____ : _____</p> </div> </div>			
	Describe the consistency of bowel movement 1 hard lumps 2 lumpy sausage 3 cracked sausage 4 smooth sausage 5 soft lumps 6 Mushy 7 watery	Describe the Ease of Passage of bowel movement 1 Manual Disimpaction 2 Enema needed 3 Straining needed 4 Normal 5 Urgent w/pain 6 Urgent w/pain 7 Incontinent	Did you feel like you completely emptied your bowels? 1 no 2 yes
1			
2			
3			
4			
5			
6			
7			

Have you had any unusual negative events today? <div style="float: right;"> No <input type="checkbox"/> Yes <input type="checkbox"/> <i>(complete below)</i> </div>			
Event _____	Mild / Moderate / Severe	Resolved / Ongoing	
Have you taken any medications other than those you routinely use today? <div style="float: right;"> No <input type="checkbox"/> Yes <input type="checkbox"/> <i>(complete below)</i> </div>			
Medication _____	Medication _____	Medication _____	
Dose _____	Dose _____	Dose _____	
Frequency _____	Frequency _____	Frequency _____	

DAILY DIARY

Please indicate how severe on average your symptoms of IBS were today by placing one vertical slash mark (/) on the scales below:

|_____|
No abdominal pain **Worst pain imaginable**

|_____|
No abdominal bloating **Worst bloating imaginable**

|_____|
No flatulence **Worst flatulence imaginable**

|_____|
No urgency **Worst urgency imaginable**

Please indicate how severe the most intense abdominal pain you experienced today was by circling one of the following responses :

- 0 None**
- 1 Mild**
- 2 Moderate**
- 3 Severe**
- 4 Very Severe**

Abridged Bowel Disease Questionnaire adapted from Talley, 1990

1. What is your current height (without shoes and to the nearest inch)? ____feet ____inches
2. What is your weight (without clothes and to the nearest pounds)? _____pounds

INSTRUCTIONS: Please complete this survey by placing a tick ✓ in ONE box for each question, or by providing one answer.

3. In the last 3 months, have you been troubled by pain or discomfort in your stomach, belly, or tummy?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

4. In the last 3 months, have you been troubled by feeling full soon after starting to eat so that you could not finish your normal meal?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

5. In the last 3 months, after having normal meals, have you been troubled by an unpleasant feeling of food staying in your stomach?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

6. In the last 3 months, have you been troubled by bloating (feeling as if your stomach or abdomen was swollen)?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

7. In the last 3 months, have you been troubled by acid regurgitation (a sour or acid tasting fluid at the back of your throat)?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

8. In the last 3 months, have you been troubled by heartburn (a burning pain or discomfort behind the breastbone rising up towards the throat)?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

9. In the last 3 months, have you been troubled by nausea (wanting to vomit)?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

10. In the last 3 months, have you been troubled by vomiting?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

11. In the last 3 months, have you been troubled by difficulty swallowing, where solid food or liquids stick on the way down?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

12. In the last 3 months, have you been troubled by a feeling of a blockage in the anus (back passage) which made it difficult for you to pass bowel movements (stool)?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

13. In the last 3 months, have you had more than 3 bowel movements (stools) each DAY?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

14. In the last 3 months, have you had fewer than 3 bowel movements each WEEK?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

15. In the last 3 months, have you been troubled by lumpy or hard bowel movements?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

16. In the last 3 months, have you been troubled by loose or watery bowel movements?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

17. In the last 3 months, have you been troubled by an urgent need to have a bowel movement that made you rush to a toilet?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

18. In the last 3 months, have you been troubled by leaking of bowel movements (accidents)?

Not at all ☐ Rarely ☐ Sometimes ☐ Often ☐ Very Often ☐

19. Have you ever used any medication(s) to try and lose weight?

No ☐

Yes ☐

↓
If YES, which medication(s)?

Sign _____ Date _____

BASELINE CHARACTERIZATION OF DETAILED GI SYMPTOMS

A STUDY OF GASTROINTESTINAL SYMPTOMS IN IRRITABLE BOWEL SYNDROME

This study is being done to provide a better understanding of gastrointestinal symptoms in people with IBS. Please answer ALL questions. If you are uncertain, please write down your best guess. It is easy to miss questions, so *please check that you haven't left any out as you go*. If you wish to comment on any questions or qualify your answers, use the space in the margins; these comments will be read and taken into account.

All information provided will be kept confidential.

Thank you for your help.

Reply to:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

**First we would like to ask you some questions about TROUBLE SWALLOWING
(a feeling that food sticks in your throat or chest) in the last year.**

1. Have you had difficulty swallowing in the last year? (Check one)

1 ☐ No →

Please go to question 9 on PAGE 2.

2 ☐ Yes →

Please answer the following questions.



**2. When in your life did this trouble swallowing FIRST begin, as close as you can recall?
(Check one)**

- 1 ☐ In the last 6 months
- 2 ☐ 7 months to 1 year ago
- 3 ☐ More than 1 year to 2 years ago
- 4 ☐ More than 2 years to 5 years ago
- 5 ☐ More than 5 years to 10 years ago
- 6 ☐ More than 10 years to 20 years ago
- 7 ☐ More than 20 years ago

3. How many times have you had this trouble swallowing in the last year? (Check one)

- 1 ☐ Less than once a month
- 2 ☐ About once a month
- 3 ☐ About once a week
- 4 ☐ Several times a week
- 5 ☐ Daily

4. How bad is your trouble swallowing usually? (Check one)

- 1 ☐ MILD - can be ignored if I don't think about it
- 2 ☐ MODERATE - cannot be ignored, but does not affect my life-style
- 3 ☐ SEVERE - affects my life-style
- 4 ☐ VERY SEVERE - markedly affects my life-style

5. Does it hurt (is it painful) when you swallow? (Check one)

- 1 ☐ No
- 2 ☐ Yes

Please check that all questions that apply to you have been answered.

6. What do you have trouble swallowing? (Check one)

- 1 ☐ Both solid foods and liquids
- 2 ☐ Solid foods only
- 3 ☐ Liquids only

7. Has your trouble swallowing gotten progressively worse in the last year? (Check one)

- 1 ☐ Yes, rapidly worse
- 2 ☐ Yes, slowly worse
- 3 ☐ No, has not gotten worse

8. Does your trouble swallowing come and go so that there are times when you have no trouble no matter what you eat? (Check one)

- 1 ☐ No
- 2 ☐ Yes

Next, we would like to ask you some questions about heartburn in the last year.

9. Have you had a burning pain or discomfort behind the breast bone in your chest in the last year?
(Please do NOT count pain in your stomach or pain from heart trouble.) (Check one)

- 1 ☐ No →

Please go to question 16 on PAGE 3.

- 2 ☐ Yes →

Please answer the following questions.



In this survey the term "heartburn" will be used to mean a burning pain or discomfort behind the breast bone in your chest. When answering these questions, please do not count any other sensations as "heartburn".

10. When in your life did this heartburn FIRST begin, as close as you can recall? (Check one)

- 1 ☐ In the last 6 months
- 2 ☐ 7 months to 1 year ago
- 3 ☐ More than 1 year to 2 years ago
- 4 ☐ More than 2 years to 5 years ago
- 5 ☐ More than 5 years to 10 years ago
- 6 ☐ More than 10 years to 20 years ago
- 7 ☐ More than 20 years ago

Please check that all questions that apply to you have been answered.

11. How many times have you had heartburn in the last year? (Check one)

- 1 ☐ Less than once a month
- 2 ☐ About once a month
- 3 ☐ About once a week
- 4 ☐ Several times a week
- 5 ☐ Daily

12. How bad is your heartburn usually? (Check one)

- 1 ☐ MILD - can be ignored if I don't think about it
- 2 ☐ MODERATE - cannot be ignored, but does not affect my life-style
- 3 ☐ SEVERE - affects my life-style
- 4 ☐ VERY SEVERE - markedly affects my life-style

13. Has your heartburn awakened you at night in the last year? (Check one)

- 1 ☐ No
- 2 ☐ Yes

NOTE: When we say "often" we mean more than 25% of the time in the last year.

14. Does your heartburn often travel up toward your neck? (Check one)

- 1 ☐ No
- 2 ☐ Yes

15. Is your heartburn often made better (eased) by taking antacids (like Amphojel, AlternaGEL, Gaviscon, Maalox, Mylanta, Riopan, Roloids or Tums)? (Check one)

- 1 ☐ No
- 2 ☐ Yes
- 3 ☐ I have not taken antacids for heartburn

We would now like to ask you about other complaints you have had in the last year.

16. How many times have you had a feeling of WANTING TO THROW UP (nausea) in the last year? (Check one)

- 1 ☐ None
- 2 ☐ Less than once a month
- 3 ☐ About once a month
- 4 ☐ About once a week
- 5 ☐ Several times a week
- 6 ☐ Daily

Please check that all questions that apply to you have been answered.

17. How many times have you ACTUALLY THROWN UP (vomited) in the last year? (Check one)

- 1 ☐ None
- 2 ☐ Less than once a month
- 3 ☐ About once a month
- 4 ☐ About once a week
- 5 ☐ Several times a week
- 6 ☐ Daily

18. Have you thrown up (vomited) bright red blood in the last year? (Check one)

- 1 ☐ No
- 2 ☐ Yes

19. Has your food come back up into your mouth or throat in the last year? (Please do not include vomiting) (Check one)

- 1 ☐ No
- 2 ☐ Yes

NOTE: When we say "often" we mean more than 25% of the time in the last year.

20. Have you often been troubled by burping (belching) up gas through the mouth in the last year? (Check one)

- 1 ☐ No
- 2 ☐ Yes

21. Have you often been troubled by hiccups in the last year? (Check one)

- 1 ☐ No
- 2 ☐ Yes

22. Have you lost weight in the last year without deliberately dieting? (Check one)

- 1 ☐ No
- 2 ☐ Less than 7 lbs.
- 3 ☐ 7 lbs. or more

23. Is your appetite in the last year compared with before: (Check one)

- 1 ☐ Decreased?
- 2 ☐ About the same?
- 3 ☐ Increased?

Please check that all questions that apply to you have been answered.

24. Have you often lost your appetite and felt full soon after starting to eat so that you could not finish a normal meal in the last year? (Check one)

- 1 ☐ No
2 ☐ Yes

Next, we would like to ask you some questions about stomach, belly or tummy pain in the last year.

25. Have you had an ache or pain in your stomach or belly (gut) in the last year? (Please do NOT count cramps or pain with menstrual periods, heartburn, or chest pain.) (Check one)

- 1 ☐ No →

Please go to question 45 on PAGE 8.

- 2 ☐ Yes →

Please answer the following questions.



Stomach or belly pain can be difficult to describe and sometimes more than one type of pain can occur. Please think about the usual or primary type of pain you have. We would like to ask you some questions only about the USUAL or PRIMARY pain in your stomach or belly.

26. Have you had this same ache or pain more than SIX times in the last year? (Check one)

- 1 ☐ No
2 ☐ Yes

27. How bad is the ache or pain *usually*? (Check one)

- 1 ☐ MILD - can be ignored if I don't think about it
2 ☐ MODERATE - cannot be ignored, but does not affect my life-style
3 ☐ SEVERE - affects my life-style
4 ☐ VERY SEVERE - markedly affects my life-style

28. Does the usual ache or pain EVER WAKE YOU FROM SLEEP AT NIGHT? (Check one)

- 1 ☐ No
2 ☐ Yes

29. Does this pain come and go periodically? (Periodically here means periods of at least a month with no pain, with periods in between of weeks to months when there is pain.) (Check one)

- 1 ☐ No
2 ☐ Yes

Please check that all questions that apply to you have been answered.

30. How many times did you get this pain in the last year? (Check one)

- 1 ☐ Less than once a month
- 2 ☐ About once a month
- 3 ☐ About once a week
- 4 ☐ Several times a week
- 5 ☐ Daily

31. When this pain occurs, how long does it usually last? (Check one)

- 1 ☐ Less than 30 minutes
- 2 ☐ 30 minutes to 2 hours
- 3 ☐ More than 2 hours to 6 hours
- 4 ☐ More than 6 hours

32. When in your life did this ache or pain FIRST begin as close as you can recall? (Check one)

- 1 ☐ In the last 6 months
- 2 ☐ 7 months to 1 year ago
- 3 ☐ More than 1 year to 2 years ago
- 4 ☐ More than 2 years to 5 years ago
- 5 ☐ More than 5 years to 10 years ago
- 6 ☐ More than 10 years to 20 years ago
- 7 ☐ More than 20 years ago

33. Does this ache or pain often occur BEFORE meals or when hungry? (Check one)

- 1 ☐ No
- 2 ☐ Yes

NOTE: When we say "often" we mean more than 25% of the time in the last year.

34. Does this ache or pain often occur IMMEDIATELY AFTER (less than 30 minutes) meals? (Check one)

- 1 ☐ No
- 2 ☐ Yes

35. Does this ache or pain often occur 30 minutes to 2 hours AFTER meals? (Check one)

- 1 ☐ No
- 2 ☐ Yes

36. Is this pain often made BETTER (relieved) by burping (bringing up air through the mouth)? (Check one)

- 1 ☐ No
- 2 ☐ Yes

Please check that all questions that apply to you have been answered.

37. Is this pain often made BETTER by having a bowel movement? (Check one)

- 1 ☐ No
- 2 ☐ Yes

38. Is this pain often made BETTER by eating? (Check one)

- 1 ☐ No
- 2 ☐ Yes

39. Is this pain often made BETTER by taking antacids (like Tums, Riopan, Mylanta, Maalox, Gaviscon or Roloids)? (Check one)

- 1 ☐ No
- 2 ☐ Yes
- 3 ☐ I don't take antacids

40. Is this pain often made WORSE by food or milk? (Check one)

- 1 ☐ No
- 2 ☐ Yes

41. Do you often have MORE bowel movements when this pain begins? (Check one)

- 1 ☐ No
- 2 ☐ Yes

42. Do you often have LOOSER bowel movements (stools) when this pain begins? (Check one)

- 1 ☐ No
- 2 ☐ Yes

43. Do you often feel bloated and actually see your belly swell up? (Check one)

- 1 ☐ No
- 2 ☐ Yes

44. Have you seen MUCUS in your stools in the last year (that is, white or green slimy material)? (Check one)

- 1 ☐ No
- 2 ☐ Yes

Please check that all questions that apply to you have been answered.
--

An important purpose of this study is to learn about bowel habits in the community in the last year.

45. In the last year, how regular were your bowel movements? (Check one)

- 1 ☐ Often had constipation (more than 25% of the time)
- 2 ☐ Sometimes had constipation (less than 25% of the time)
- 3 ☐ Alternating diarrhea and constipation
- 4 ☐ Sometimes diarrhea (less than 25% of the time)
- 5 ☐ Often had diarrhea (more than 25% of the time)
- 6 ☐ Usually normal

46. What is the longest number of days you have ever gone without having a bowel movement in the last year? (Check one)

- 1 ☐ 2 days or less
- 2 ☐ More than 2 to 4 days
- 3 ☐ More than 4 days to 1 week
- 4 ☐ More than 1 to 2 weeks
- 5 ☐ More than 2 weeks

47. How many bowel movements do you usually have in a WEEK? (Check one)

- 1 ☐ 1 or less
- 2 ☐ 2
- 3 ☐ 3-4
- 4 ☐ 5-8
- 5 ☐ 9-12
- 6 ☐ 13-16
- 7 ☐ 17-21
- 8 ☐ 22-26
- 9 ☐ More than 26

48. In the last year, did you need to take anything to help you have a bowel movement (such as laxative, enema, or suppository, but not including fiber products)? (Check one)

- 1 ☐ No
- 2 ☐ Yes, sometimes (less than 25% of the time)
- 3 ☐ Yes, often (more than 25% of the time)
- 4 ☐ Yes, usually (more than 75% of the time)

If yes, what did you take? _____

Please check that all questions that apply to you have been answered.

49. In the last year, have you needed to strain a lot (for more than 1 to 2 minutes) to have a bowel movement? (Check one)

- 1 ☐ No
- 2 ☐ Yes, sometimes (less than 25% of the time)
- 3 ☐ Yes, often (more than 25% of the time)
- 4 ☐ Yes, usually (more than 75% of the time)

50. How severe was your straining with bowel movements in the last year? (Check one)

- 1 ☐ I never strain with bowel movements
- 2 ☐ Very mild
- 3 ☐ Mild
- 4 ☐ Moderate
- 5 ☐ Severe
- 6 ☐ Very severe

51. In the last year, have your stools been loose or watery? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time)
- 3 ☐ Often (more than 25% of the time)
- 4 ☐ Usually (more than 75% of the time)

52. In the last year, have your stools been hard? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time)
- 3 ☐ Often (more than 25% of the time)
- 4 ☐ Usually (more than 75% of the time)

53. In the last year, after finishing a bowel movement, have you felt there was still stool that needs to be passed? (Check one)

- 1 ☐ No
- 2 ☐ Yes

54. In the last year, have you experienced an urgent need to open your bowels that made you rush to the toilet? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time)
- 3 ☐ Often (more than 25% of the time)
- 4 ☐ Usually (more than 75% of the time)

55. Have you noticed ANY BLOOD in your stools or in the toilet bowl in the last year? (Check one)

- 1 ☐ No
- 2 ☐ Yes

Please check that all questions that apply to you have been answered.
--

56. In the last year, did you ever press your finger in or around the anus (back passage) to help a bowel movement come out? (Check one)

- 1 ☐ No
- 2 ☐ Yes

57. How much time did you usually need to spend each time on the toilet to move your bowels during the last year? (Check one)

- 1 ☐ Less than 5 minutes
- 2 ☐ 5 to 10 minutes
- 3 ☐ More than 10 minutes up to 30 minutes
- 4 ☐ More than 30 minutes up to 1 hour
- 5 ☐ More than 1 hour

58. In the last year, did you have to position yourself other than in the sitting position to help a bowel movement come out? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time)
- 3 ☐ Often (more than 25% of the time)
- 4 ☐ Usually (more than 75% of the time)

If yes, which position usually? _____

59. In the last year, did you feel there was a blockage in your rectum or anus (back passage) which made it difficult for you to pass the stool? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time)
- 3 ☐ Often (more than 25% of the time)
- 4 ☐ Usually (more than 75% of the time)

<p>Please check that all questions that apply to you have been answered.</p>

60. Have you had problems with leakage of stool (accidents or soiling because of the inability to control the passage of stool until you reached a toilet)? (Check one)

1 ☐ No

Please go to question 70 on PAGE 13.

2 ☐ Yes

Please answer the following questions.

61. In the last year, did you have to take medication (like antidiarrheals, Lomotil, Imodium AD, etc.) to prevent leakage of stool? (Check one)

1 ☐ No

2 ☐ Yes, sometimes (less than 25% of the time)

3 ☐ Yes, often (more than 25% of the time)

4 ☐ Yes, usually (more than 75% of the time)

If yes, what did you take? _____

62. When in your life did this problem with leakage of stool first begin, as close as you can recall? (Check one)

1 ☐ In the last 6 months

2 ☐ 7 months to 1 year ago

3 ☐ More than 1 year to 2 years ago

4 ☐ More than 2 years to 5 years ago

5 ☐ More than 5 years to 10 years ago

6 ☐ More than 10 years to 20 years ago

7 ☐ More than 20 years ago

63. In the last year, did you ever wear a pad to protect your underclothes from soilage or leakage of stool? (Check one)

1 ☐ Never

2 ☐ Sometimes (less than 25% of the time)

3 ☐ Often (more than 25% of the time)

4 ☐ Usually (more than 75% of the time)

64. In the last year, when was the leakage of stool most frequent? (Check one)

1 ☐ While awake

2 ☐ While asleep

3 ☐ There was no difference in leakage while asleep or awake

Please check that all questions that apply to you have been answered.

65. When leakage of stool has occurred in the last year, did you have problems with leakage of liquid or runny stool? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time that leakage occurred)
- 3 ☐ Often (more than 25% of the time that leakage occurred)
- 4 ☐ Usually (more than 75% of the time that leakage occurred)

66. When leakage of stool has occurred in the last year, did you have problems with leakage of solid, or formed stool? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time that leakage occurred)
- 3 ☐ Often (more than 25% of the time that leakage occurred)
- 4 ☐ Usually (more than 75% of the time that leakage occurred)

67. When these "accidents" with leakage of stool occurred in the last year, how much stool typically leaked out? (Check one)

- 1 ☐ A small amount, with a stain about the size of a quarter
- 2 ☐ Moderate amounts (often requiring a change of pad or underwear)
- 3 ☐ Large bowel movements of liquid stool (often requiring a complete change of clothes)
- 4 ☐ Solid or formed stool

68. In the last year, have you been able to tell when this leakage of stool was about to occur? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time)
- 3 ☐ Often (more than 25% of the time)
- 4 ☐ Usually (more than 75% of the time)

69. In the last year, have you had difficulty telling the difference between the need to pass gas and the need to pass stool? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time)
- 3 ☐ Often (more than 25% of the time)
- 4 ☐ Usually (more than 75% of the time)

Please check that all questions that apply to you have been answered.
--

Questions 70 - 74 are for women, if you are a man, please go to Question 75 on page 14.

70. In the last year, did you ever press your finger in or around the vagina (front passage) to help a bowel movement come out? (Check one)

- 1 ☐ No
2 ☐ Yes

71. Have you ever given birth to a child? (Check one)

- 1 ☐ No
2 ☐ Yes

If YES, how many children? _____
number by vaginal delivery? _____
number by Cesarean section? _____
number for which forceps were used? _____

72. Have you had any injuries to your anus (back passage) during childbirth which required surgical repair? (Check one)

- 1 ☐ No
2 ☐ Yes
3 ☐ I have never given birth

If YES, what repair was done? _____

73. Have you ever had a protrusion of the rectum through the opening of the vagina (called a rectocele)? (Check one)

- 1 ☐ No
2 ☐ Yes

If YES, when? _____

74. Have you ever had a protrusion of the rectum through the anus (called a rectal prolapse)? (Check one)

- 1 ☐ No
2 ☐ Yes

If YES, when? _____

Please check that all questions that apply to you have been answered.

75. In the last year, have you had slow leakage, or dribbling, or urine throughout the day? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time)
- 3 ☐ Often (more than 25% of the time)
- 4 ☐ Usually (more than 75% of the time)

76. In the last year, have you worn a pad to protect your underclothes from leakage of urine? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time)
- 3 ☐ Often (more than 25% of the time)
- 4 ☐ Usually (more than 75% of the time)

77. In the last year, have you had leakage of urine when you coughed or sneezed? (Check one)

- 1 ☐ Never
- 2 ☐ Sometimes (less than 25% of the time)
- 3 ☐ Often (more than 25% of the time)
- 4 ☐ Usually (more than 75% of the time)

78. In the last year, when leakage of urine has occurred, were you aware of the need to urinate before the leakage occurred? (Check one)

- 1 ☐ I have no leakage of urine throughout the day
- 2 ☐ Never
- 3 ☐ Sometimes (less than 25% of the time)
- 4 ☐ Often (more than 25% of the time)
- 5 ☐ Usually (more than 75% of the time)

Please answer the following questions regarding other urinary symptoms.

79. During the last month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating? (Check one)

- 1 ☐ Not at all
- 2 ☐ Less than 1 time in 5
- 3 ☐ Less than half the time
- 4 ☐ About half the time
- 5 ☐ More than half the time
- 6 ☐ Almost always

Please check that all questions that apply to you have been answered.

80. During the last month or so, how often have you had to push or strain to begin urination? (Check one)

- 1 ☐ Not at all
- 2 ☐ Less than 1 time in 5
- 3 ☐ Less than half the time
- 4 ☐ About half the time
- 5 ☐ More than half the time
- 6 ☐ Almost always

81. During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning? (Check one)

- 1 ☐ Not at all
- 2 ☐ Less than 1 time in 5
- 3 ☐ Less than half the time
- 4 ☐ About half the time
- 5 ☐ More than half the time
- 6 ☐ Almost always

To help interpret the results of this survey, we would like to ask some questions about your activities, habits and work. Please be assured that all information will be kept strictly confidential.

82. Please indicate the IMPORTANCE of each of these ACTIVITIES to you in the LAST YEAR.
(Check one answer on each line)

Please check that all questions that apply to you have been answered.

83. Next, please indicate whether ANY problems with your BOWEL FUNCTION have affected each of these same activities in the LAST YEAR. (Do NOT include problems related to TEMPORARY illnesses, flu, etc.) (Check one answer on each line.)

84. Next, please indicate whether problems with LEAKAGE OF STOOL have affected each of these same activities in the LAST YEAR. (Check one answer on each line.)

85. Did you ever smoke cigarettes regularly (at least 1 cigarette per day for at least 30 days)? (Check one)

- 1 ☐ No
2 ☐ Yes

<p>At what age did you start? _____ years</p> <p>When smoking the heaviest, how many packs did you</p> <p>Smoke per day? _____</p> <p>How many packs per day do you currently smoke? _____</p> <p>If you stopped smoking, at what age did you stop? _____</p>

Next, there is a question about drinks that contain alcohol (that is, beer, wine, or other liquors like whiskey, vodka, gin, or brandy). One drink is equal to a can of beer, a glass of wine, or shot of spirits.

86. How many drinks a WEEK have you had on average in the last year? (Check one)

- 1 ☐ None
- 2 ☐ 1 to 2 drinks a week
- 3 ☐ 3 to 6 drinks a week
- 4 ☐ 7 to 10 drinks a week
- 5 ☐ More than 10 drinks a week

87. Do you drink coffee? (Check one)

- 1 ☐ No
- 2 ☐ Yes

Decaffeinated or regular usually? _____
How many cups per day usually? _____
Does drinking coffee bring on or worsen your heartburn?
1 ☐ No 2 ☐ Yes

88. Current marital status: (Check one)

- 1 ☐ Married
- 2 ☐ Single
- 3 ☐ Widowed
- 4 ☐ Divorced
- 5 ☐ Separated
- 6 ☐ Other

89. Are you presently: (Check one)

- 1 ☐ Employed
- 2 ☐ Unemployed
- 3 ☐ Retired
- 4 ☐ Full-time homemaker
- 5 ☐ Full-time student
- 6 ☐ Disabled

90. Please indicate your educational training. (Check one)

- 1 ☐ Professional training beyond college
- 2 ☐ College graduate (4 years)
- 3 ☐ Some college
- 4 ☐ High school graduate
- 5 ☐ 10-11 years of school, include some high school
- 6 ☐ 7-9 years of school, grade school graduate
- 7 ☐ Under 7 years of grade school

91. Indicate your racial background (optional):

- 1 ☐ Caucasian
- 2 ☐ Hispanic
- 3 ☐ African American
- 4 ☐ Native American
- 5 ☐ Asian/Pacific Islander
- 6 ☐ Other _____
- 7 ☐ Unknown

Next, we would like to ask you questions about your general health.

92. Do the muscles in your arms or legs feel as though their strength has decreased? (Check one)

- 1 ☐ No
- 2 ☐ Yes

93. Do you get muscle cramps or "Charley horse" in your arms or legs, particularly during exercise? (Check one)

- 1 ☐ No
- 2 ☐ Yes

94. Do you have any numbness, heat sensation, or prickly feeling in any part of your body? (Check one)

- 1 ☐ No
- 2 ☐ Yes

95. Do you faint on changing your position? (Check one)

- 1 ☐ No
- 2 ☐ Yes

96. Do you have blurring of vision with prolonged reading? (Check one)

- 1 ☐ No
- 2 ☐ Yes

97. Do you have episodes of overheating because you sweat insufficiently? (Check one)

- 1 ☐ No
- 2 ☐ Yes

98. Do you sweat on your face after eating cheese or red wine? (Check one)

- 1 ☐ No
- 2 ☐ Yes

Please check that all questions that apply to you have been answered.

99. Do you feel your heart racing or pounding with force? (Check one)

- 1 ☐ No
- 2 ☐ Yes

100. Do you have chest pain that is brought on during exercise? (Check one)

- 1 ☐ No
- 2 ☐ Yes

101. Do your legs swell and does your finger leave an imprint if you press on your ankle or foot? (Check one)

- 1 ☐ No
- 2 ☐ Yes

102. Do you have cloudy or blood-stained urine? (Check one)

- 1 ☐ No
- 2 ☐ Yes

103. Have you needed laser treatment of your eyes? (Check one)

- 1 ☐ No
- 2 ☐ Yes

104. Have you needed treatment for cataract? (Check one)

- 1 ☐ No
- 2 ☐ Yes

It is important for us to know about the medications that you are taking.

105. Are you taking any of the following medications? (Please check those you are taking)

- 1 ☐ Aspirin, Ibuprofen, Advil, Motrin, Voltaren, Naprosyn
- 2 ☐ Antacids
- 3 ☐ Zantac, Axid, Pepcid, Tagamet
- 4 ☐ Prilosec, Prevacid
- 5 ☐ Propulsid
- 6 ☐ Laxatives
- 7 ☐ Imodium
- 8 ☐ Lomotil
- 9 ☐ Cardizem, Isoptin, Verapamil, Adalat, Procardia
- 10 ☐ Clonidine, Catapres
- 11 ☐ Insulin

Please check that all questions that apply to you have been answered.

106. Please list below any other medication that you are taking:

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____

Another important purpose of this study is to learn about your previous health and visits to the doctor.

107. How many times have you visited a doctor or a physician for any reason in the last year?
(Check one)

- 1 ☐ None
2 ☐ 1 to 2 times in the last year
3 ☐ 3 to 5 times in the last year
4 ☐ 6 to 10 times in the last year
5 ☐ More than 10 times in the last year

If you have visited a doctor, why did you go? _____

108. How many times have you been hospitalized for any reason in the last year? (Check one)

- 1 ☐ None
2 ☐ 1 to 2 times in the last year
3 ☐ 3 to 5 times in the last year
4 ☐ 6 to 10 times in the last year
5 ☐ More than 10 times in the last year

If you were hospitalized, what were the reasons? _____

109. How many times in the last year have you visited your doctor or physician for problems with your bowels? (Check one)

- 1 ☐ None
2 ☐ 1 to 2 times
3 ☐ 3 to 5 times
4 ☐ 6 to 10 times
5 ☐ More than 10 times

Please check that all questions that apply to you have been answered.

110. How many times in the last year have you visited your doctor or physician for problems with leakage of stool? (Check one)

- 1 ☐ None
- 2 ☐ 1 to 2 times
- 3 ☐ 3 to 5 times
- 4 ☐ 6 to 10 times
- 5 ☐ More than 10 times

Finally, please complete the following symptoms checklist.

IMPORTANT: For each of the complaints or problems below, please indicate how often it occurred and how bothersome it was in the last year.

Write down a number from 0 to 4 for all 16 questions below in both columns.

HOW OFTEN?

- 0 Not a problem
- 1 Occurs about once a month
- 2 Occurs about once a week
- 3 Occurs several times a week
- 4 Occurs daily

HOW BOTHERSOME?

- 0 Not a problem
- 1 Slightly bothersome when occurs
- 2 Moderately bothersome when occurs
- 3 Severely bothersome when occurs
- 4 Extremely bothersome when occurs

	HOW OFTEN? (0-4):	HOW BOTHERSOME? (0-4):
1. Headaches	_____	_____
2. Backaches	_____	_____
3. Asthma (wheezing)	_____	_____
4. Trouble breathing	_____	_____
5. Insomnia (difficult sleeping)	_____	_____
6. Fatigue (tiredness)	_____	_____
7. Depression (feeling sad or blue)	_____	_____
8. General stiffness	_____	_____
9. Heart palpitations (pounding/racing)	_____	_____
10. Joint pains	_____	_____
11. Eye pain associated with reading	_____	_____
12. Dizziness	_____	_____
13. Weakness	_____	_____
14. Nervousness or shakiness	_____	_____
15. Hot or cold spells	_____	_____
16. High blood pressure	_____	_____

Please check that you have answered all 16 questions--every question should have a number from 0 to 4 in the "How Often?" and in the "How Bothersome?" columns.

Is there anything else you would like to tell us about your health problems? If so, please use this space for that purpose.

Also, any comments that may help us understand these problems better will be appreciated, either here or in a separate letter.

Please check that all questions that apply to you have been answered.

The Hospital Anxiety and Depression Questionnaire

Please read each item and **circle** the reply which best describes how you have been feeling during the past week. Don't devote too much time to your responses; your immediate reaction will probably be more accurate than a long thought out response.

1. I feel tense or 'wound up' :

Most of the time
A lot of the time
Occasionally
Not at all

2. I still enjoy the things I used to enjoy :

Definitely as much
Not quite so much
Only a little
Hardly at all

3. I get a frightened feeling, as if something awful is about to happen :

Very definitely and quite badly
Yes, but not too badly
A little, but it doesn't worry me
Not at all

4. I can laugh and see the funny side of things :

As much as I always could
Not quite so much now
Definitely not so much now
Not at all

5. Worrying thoughts go through my mind :

A great deal of the time
A lot of the time
From time to time
Only occasionally

6. I feel cheerful :

Not at all
Not often
Sometimes
Most of the time

7. I can sit at ease and feel relaxed :

Definitely
Usually
Not often
Not at all

8. I feel as if I am slowed down :

Nearly all the time
Very often
Sometimes
Not at all

9. I get a frightened feeling, like 'butterflies in the stomach' :

Not at all
Occasionally
Quite often
Very often

10. I have lost interest in my appearance :

Definitely
I don't take as much care as I should
I may not take quite as much care
I take just as much care as ever

11. I feel restless as if I have to be on the move :

Very much indeed
Quite a lot
Not very much
Not at all

12. I look forward with enjoyment to things :

As much as I ever did
Rather less than I used to
Definitely less than I used to
Hardly at all

13. I get sudden feelings of panic :

Very often indeed
Quite often
Not very often
Not at all

14. I can enjoy a good book or TV program :

Often
Sometimes
Not often
Very seldom

APPENDIX 2 (Quality of Life Questionnaire)

PARTICIPANT ID:

Please write in
TODAY'S DATE: _____
MONTH DAY YEAR

PLEASE READ THIS CAREFULLY

ON THE FOLLOWING PAGES YOU WILL FIND STATEMENTS CONCERNING BOWEL PROBLEMS (IRRITABLE BOWEL SYNDROME) AND HOW THEY AFFECT YOU.

FOR EACH STATEMENT, PLEASE CHOOSE THE RESPONSE THAT APPLIES BEST TO YOU AND **CIRCLE** THE NUMBER OF YOUR RESPONSE.

IF YOU ARE UNSURE ABOUT HOW TO RESPOND TO A STATEMENT, PLEASE GIVE THE BEST RESPONSE YOU CAN. **THERE ARE NO RIGHT OR WRONG RESPONSES.**

YOUR RESPONSES WILL BE KEPT STRICTLY CONFIDENTIAL.

IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT:

****SITE ADDRESS AND PHONE NUMBER TO BE PLACED HERE****

The IBS-QOL was developed by Donald L. Patrick, Ph.D. at The University of Washington, Douglas A. Drossman, MD at The University of North Carolina, Novartis Pharmaceuticals Corporation, and Novartis Pharma AG. Authors hold joint copyright over the IBS-QOL and all its translations.

About how you feel

Please think about your life over the **past month (last 30 days)**, and look at the statements below. Each statement has five different responses. For each statement, please circle the response that best describes your feelings.

Q1. I feel helpless because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q2. I am embarrassed by the smell caused by my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q3. I am bothered by how much time I spend on the toilet. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q4. I feel vulnerable to other illnesses because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q5. I feel fat/bloated because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q6. I feel like I'm losing control of my life because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q7. I feel my life is less enjoyable because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q8. I feel uncomfortable when I talk about my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q9. I feel depressed about my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q10. I feel isolated from others because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q11. I have to watch the amount of food I eat because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q12. Because of my bowel problems, sexual activity is difficult for me. *(Please circle one number)*
(If not applicable, please circle "NOT AT ALL")

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q13. I feel angry that I have bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q14. I feel like I irritate others because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q15. I worry that my bowel problems will get worse. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q16. I feel irritable because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q17. I worry that people think I exaggerate my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q18. I feel I get less done because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q19. I have to avoid stressful situations because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q20. My bowel problems reduce my sexual desire. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q21. My bowel problems limit what I can wear. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q22. I have to avoid strenuous activity because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q23. I have to watch the kind of food I eat because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q24. Because of my bowel problems, I have difficulty being around people I do not know well. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q25. I feel sluggish because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q26. I feel unclean because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q27. Long trips are difficult for me because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q28. I feel frustrated that I cannot eat when I want because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q29. It is important to be near a toilet because of my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

Q30. My life revolves around my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q31. I worry about losing control of my bowels. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q32. I fear that I won't be able to have a bowel movement. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q33. My bowel problems are affecting my closest relationships. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 A GREAT DEAL

Q34. I feel that no one understands my bowel problems. *(Please circle one number)*

- 1 NOT AT ALL
- 2 SLIGHTLY
- 3 MODERATELY
- 4 QUITE A BIT
- 5 EXTREMELY

APPENDIX 3 Prohibited Concomitant Medication

The following medications and medication combinations are strong inhibitors of CYP3A4. This list should not be considered all-inclusive. As described in the study protocol, concomitant use of strong CYP3A4 inhibitors is prohibited. Individual drug labels should be reviewed for specific information on propensity to cause strong inhibition of the CYP3A4 enzyme for a specific compound.

Strong CYP3A4 inhibitors
Boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, nefazodone, nelfinavir, mifepristone, mibefradil, telithromycin, troleandomycin

The following medications and supplements are moderate to strong inducers of CYP3A4. As described in the study protocol, concomitant use of moderate to strong CYP3A4 inducers is prohibited. This list should not be considered all-inclusive. Individual product labels should be reviewed for specific information on propensity to cause moderate to strong induction of the CYP3A4 enzyme for a specific compound.

Strong CYP3A4 inducers
Apalutamide, avasimibe, carbamazepine, phenytoin, rifampin, rifapentine, St. John's Wort

Moderate CYP3A4 inducers
Bosentan, efavirenz, etravirine, lopinavir, modafinil, nafcillin, rifabutin, phenobarbital

APPENDIX 4: Contraception

The criteria below specify the reproductive requirements for including female participants.

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below).

OR

- Is a WOCBP and agrees to use an acceptable contraceptive method during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea or oligomenorrhea) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

- Documented hysterectomy;
- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

- A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
- A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
 - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
 - Oral;
 - Intravaginal;
 - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
 - Oral;
 - Injectable.
8. Sexual abstinence

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Other Effective Methods

1. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
2. Male or female condom, with or without spermicide.
3. Cervical cap, diaphragm, or sponge with spermicide.
4. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).