CLINICAL PROTOCOL

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vibegron Administered Orally for 12 Weeks to Women with Irritable Bowel Syndrome

Protocol Number:	URO-901-2001
Version Number:	4.0 (Amendment 3) Replaces Amendment 2 (Version 3.0; dated 30 August 2019)
Product:	Vibegron (URO-901, RVT-901, MK-4618, KRP-114V)
Development Phase:	2
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Approval Date:	19 November 2019
Sponsor Signatory:	[redacted]

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Study Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vibegron Administered Orally for 12 Weeks to Women with Irritable Bowel Syndrome

Protocol Number: URO-901-2001

This protocol has been approved by a representative of Urovant Sciences GmbH. The following signature documents this approval.

[redacted]

Date

INVESTIGATOR STATEMENT

Study URO-901-2001: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vibegron Administered Orally for 12 Weeks to Women with Irritable Bowel Syndrome

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date (DD/MON/YYYY)	Site Number

PROTOCOL AMENDMENT 3 - SUMMARY OF CHANGES

This protocol was amended to include the following notable changes:

- Justification for Dose (Section 4.3)
    - Added data from Phase 2 and 3 studies showing that doses up to 100 mg (including 75mg) of vibegron vs. placebo were safe and efficacious in patients with OAB up to 52 weeks.
- Inclusion criteria (Section 5.1) and Section 10.2
    - Made fecal calprotectin testing optional per investigator's discretion, reserving evaluation only in subjects with a strong suspicion for inflammatory bowel disease (IBD) (eg, IBD family history in a 1st degree relative, other genetic factors, etc)
- Inclusion criteria (Section 5.1):
    - Removed C-reactive protein (CRP) testing as an eligibility requirement for all subjects
    - Updated diary completion for screening to "any 5 days out of 7 days at baseline prior to Day 1 Randomization"
    - Removed the IBS-D diarrhea criterion (Bristol Stool Scale Type 6 or 7)
- Exclusion criteria (Section 5.2), Section 6.5.1, 10.7.2, and Schedule of Assessments
    - For subjects who had a positive urine drug screen at Visit 1 due to a prohibited concomitant medication, the urine drug screen must be repeated at Visit 2 to determine if sufficient washout of the prohibited concomitant medication has occurred and to confirm eligibility. The urine drug screen does not need to be re-tested at Visit 2 if the initial positive result at Visit 1 was due to a permitted concomitant medication based on the clinical judgment of the investigator.
- Table 6-2 Medications Permitted at Stable Doses
    - Added class of medications: Antispasmodics/Smooth muscle relaxants and Peppermint Oil
- Subject Stratification
    - Increased cap on IBS-M subjects from $n \leq 40$ (20%) to $n \leq 100$ (50%)
- Statistics Considerations (Section 9):
    - Removed the formal hypothesis testing. The primary objective is to estimate the treatment effect of each group. Nominal p-values will be provided for descriptive purposes
    - Updated the sample size section accordingly based on the requirement that 50% of the subjects be IBS-M
    - Added two additional analysis populations: Full analysis set (FAS): FAS-D and FAS-M, which are each subsets of FAS.
    - Added that an interim analysis may be performed

PROTOCOL AMENDMENT 2 - SUMMARY OF CHANGES

This protocol was amended to include the following notable changes:

- Changed the timing of the Safety Follow-up telephone call from 21 days to 14 days after the last dose of study drug (with −7 day window), and clarified that the Safety Follow-up assessment applies only to randomized subjects (Sections 1.3, 8.4.3, 10.7.8 and elsewhere for consistency)
- Clarified that the scheduled urine assessment at Visits 1, 3, 4, 5, 6, and 7 will be a urine dipstick, with urinalysis and culture/sensitivity testing performed if the urine dipstick results suggest a urinary tract infection; also clarified that a urine dipstick should be performed when a subject presents at an Unscheduled Visit with symptoms of urinary tract infection (with subsequent urinalysis and culture/sensitivity testing if warranted) (Sections 1.3 and 10.2)
- Inclusion criteria (Section 5.1):
  - Clarified acceptable fecal calprotectin level (≤ 150 mcg/g) and acceptable C-reactive protein level (< 17 mg/L) in subjects with irritable bowel syndrome (IBS)
- Exclusion criteria (Section 5.2):
  - Provided exclusionary timeframes for both uncomplicated and complicated prior appendectomy
  - Clarified that acute, symptomatic cholecystitis or symptomatic cholelithiasis within the past 6 months is exclusionary
  - Removed known or suspected human immunodeficiency virus or acquired immunodeficiency syndrome as an exclusion
- Endpoints (Section 3):
  - Primary: Clarified the primary endpoint for consistency with Food and Drug Administration guidance for clinical evaluation of IBS treatments
  - Secondary
    - Clarified the Week 12 Global Improvement Scale (GIS) endpoint as the proportion of GIS responders
    - Added the endpoint of proportion of IBS subjects with predominantly diarrhea (IBS-D) who are abdominal pain intensity (API) weekly responders with ≥ 40% improvement
    - Added the endpoint of proportion of IBS-D subjects who are API weekly responders with ≥ 50% improvement
  - Exploratory
    - [redacted]

- Changed planned number of sites from approximately 30 to approximately 40 (Section 4.1)
- Concomitant medications (Section 6.5):
  - Removed nonsteroidal anti-inflammatory drugs and beta antagonists from the list of prohibited medications
  - Changed washout period for mu-opioid receptor agonists from 3 months to 1 month
  - Clarified that systemic cannabidiol is prohibited
  - Added stable doses of antihypertensives to the list of permitted medications
  - Clarified that rescue medications should only be used beginning at Day 1 (Visit 3)
  - Added low-dose acetaminophen (500 mg three times daily or less) as a rescue medication for pain
  - Changed the dose of the rescue medication ibuprofen from 200 mg twice daily or less to 400 mg twice daily or less
- Discontinuation of Study Drug (Section 7)
  - Clarified assessments and forms that should be completed for subjects who are screen failures or run-in failures
  - Removed Screen Failure and Run-in Failure as reasons for discontinuation of study drug for randomized subjects
- Clarified that rescreening may occur beyond the 5-week Screening Period and that the Sponsor's designated Medical Monitor, Sponsor, or its designee must be consulted and approve rescreens (Section 5.4 and elsewhere for consistency)
- Statistical Methods (Section 9)
  - Clarified definition of Full Analysis Set to require at least 1 baseline diary assessment and at least 1 post-randomization diary entry instead of 1 evaluable change in abdominal pain response
  - Deleted process for imputation of missing Week 12 data because it is not applicable
  - Updated significance level for primary hypothesis to 0.10 for consistency with statistical methods
  - Added a Per-Protocol Set analysis
- Clarified that abnormal screening laboratory values should not be documented as adverse events (Section 10.3)

In addition, administrative updates (eg, footer dates, abbreviations), corrections of minor typographical errors, editorial changes, clarifications, and/or stylistic and formatting revisions have been made to improve clarity and consistency throughout the document.

PROTOCOL AMENDMENT 1 - SUMMARY OF CHANGES

This protocol was amended to include the following notable changes:

- Specified eluxadoline as a prohibited medication, resulting in the following changes:
  - removed Inclusion Criterion #6 regarding the stability of eluxadoline dosage regimen for applicable subjects
  - removed "**and** currently receiving eluxadoline" from Exclusion Criterion #18
  - removed "current eluxadoline use (yes vs no)" as a stratification factor
  - added "Mu-opioid receptor agonist/eluxadoline" to Table 6-1 (Prohibited Medications)
  - removed "Mu-opioid receptor agonist/eluxadoline" from Table 6-2 (Medications Permitted at Stable Doses)
- Added body temperature to list of vital sign assessments (Section 1.3, Section 8.3.2, and Section 10.7).
- Clarified that subjects will be supplied with stool sample collection kits if they are unable to provide a stool sample during the Screening visit (Section 1.3 and Section 10.7.1).
- [redacted]
- Added a Data Safety Monitoring Board (DSMB) to assess safety aspects of this study, with 3 planned DSMB data reviews after 25%, 50%, and 75% of randomized subjects have received study drug and completed study visits through Week 4 (Visit 5) (Section 4.1 and Section 9.6).
- Changed maximum allowable enrollment for subjects with irritable bowel syndrome with mixed episodes of diarrhea and constipation (IBS-M) from 40% to 20% of the total study population (Section 4.1).
- Reduced total target enrollment from 350 subjects to 200 subjects (and updated expected evaluable subjects from 140 subjects to 90 subjects per treatment group) (Section 4.1 and Section 9.2).
- Reduced planned number of sites from 50 to approximately 30, and limited enrollment to sites in the United States (Section 4.1).
- Added "completing patient registry verification" as part of the inclusion criterion for demonstrating that subject is capable of giving informed consent (Section 5.1).
- Added "solitary rectal ulcer syndrome" to Exclusion Criterion #5 as an example of altered normal gastrointestinal anatomy (Section 5.2).
- Added clinically significant electrocardiogram (ECG) abnormality as Exclusion Criterion #22 (and renumbered subsequent criteria) (Section 5.2).

- Added to list of prohibited drug classes and provided relevant examples (Section 6.5.1).
- Added "Run-in failure" as a potential reason for termination of individual subjects (Section 7.1).
- Added definition of treatment-emergent adverse event (TEAE) to the statistical methods (Section 9.4.3.1).
- Clarified list of specific laboratory parameters to be tested (Section 10.2).
- Changed AE severity rating from a 3-point scale to a 5-point scale by adding Grade 4/life-threatening and Grade 5/fatal severity grades (Section 10.3).

In addition, administrative updates (eg, footer dates, abbreviations), corrections of minor typographical errors, editorial changes, and/or stylistic and formatting revisions have been made to improve clarity and consistency throughout the document.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vibegron Administered Orally for 12 Weeks to Women with Irritable Bowel Syndrome

Protocol Number: URO-901-2001

Brief Title: Double-blind, Placebo-controlled Study of Vibegron in Irritable Bowel Syndrome

Study Rationale:

Animal models have shown that beta-3 adrenergic receptor (β_3-AR) activation protects against gastric ulcers, inhibits castor-oil induced diarrhea, and reduces observed pain behavior [Vasina, 2008; Cellek, 2007]. Clinical studies of solabegron, a β_3-AR agonist, have shown improvement in pain among women with IBS, with no effect on gut motility in healthy subjects [Grudell, 2008; Kelleher, 2008]. Vibegron, a novel β_3-AR agonist, is in clinical development for the treatment of overactive bladder. It has been studied in approximately 2300 subjects (1840 with overactive bladder and 460 healthy subjects) and is currently being assessed in Phase 3 studies. All clinical data available to date indicate that vibegron is well tolerated.

Objectives and Endpoints (Primary and Secondary Only):

The primary study objective is to compare the effect of vibegron vs placebo in subjects with abdominal pain due to irritable bowel syndrome (IBS) with predominantly diarrhea (IBS-D) on the abdominal pain intensity (API) weekly responder rate over 12 weeks. Secondary objectives are to:

- Compare the effect of vibegron vs placebo in subjects with abdominal pain due to IBS-D or mixed episodes of diarrhea and constipation (IBS-M) on patient-reported outcomes
- Compare the effect of vibegron vs placebo in subjects with abdominal pain due to IBS-D on the API weekly responder rate over 12 weeks based on different thresholds of improvement
- Compare the effect of vibegron vs placebo in subjects with abdominal pain due to IBS-D or IBS-M on safety endpoints

The primary endpoint is the proportion of API weekly responders over 12 weeks, with an API Weekly Responder defined as a subject who experiences a decrease in the weekly average of "worst abdominal pain in the past 24 hours" scores of at least 30% compared with the baseline weekly average. Secondary endpoints are the proportion of Global Improvement Scale responders at Week 12, the proportion of IBS-D subjects who are API weekly responders with at least 40% improvement over 12 weeks, the proportion of IBS-D subjects who are API

responders with at least 50% improvement over 12 weeks, adverse events (AEs), clinical laboratory values, and vital signs.

Overall Study Design:

This study is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of vibegron in women with irritable bowel syndrome with predominantly diarrhea (IBS-D) or mixed episodes of diarrhea and constipation (IBS-M). Subjects who meet all eligibility criteria will be randomized in a 1:1 ratio to receive either vibegron 75 mg or matched placebo. Randomization will be stratified by baseline abdominal pain intensity score (< 6 vs ≥ 6 on a 0- to 10-point numeric rating scale) and IBS subtype (IBS-D vs IBS-M). Enrollment for subjects with IBS-M will be capped at 50% of the total subject population (ie, up to 50% [n=100] of the study population can be subjects with IBS-M). Stratification will be performed via central randomization across the study (not per site).

The study consists of a Screening Period (1 to 5 weeks), a single-blind placebo Run-in Period (2 weeks), a randomized double-blind Treatment Period (12 weeks), and a Safety Follow-up telephone call (approximately 2 weeks).

Number of Subjects:

In total, approximately 200 subjects will be randomized in a 1:1 ratio (100 per treatment group). At most, 50% of randomized subjects (100 subjects total [50 per treatment arm]) will have IBS-M; and at least 50% of randomized subjects (100 subjects total [50 per treatment arm]) will have IBS-D. Assuming a total of 10% of subjects will discontinue prior to Week 12 (for any reason), there will be a minimum of approximately 90 evaluable IBS-D subjects (45 per treatment group) at the end of Week 12. The sample size justification is provided in Section 9.2.

Number of Sites:

Approximately 40 sites in the United States.

Study Drug Groups and Study Duration:

Single-blind Run-in: 1 matched placebo tablet daily for 2 weeks

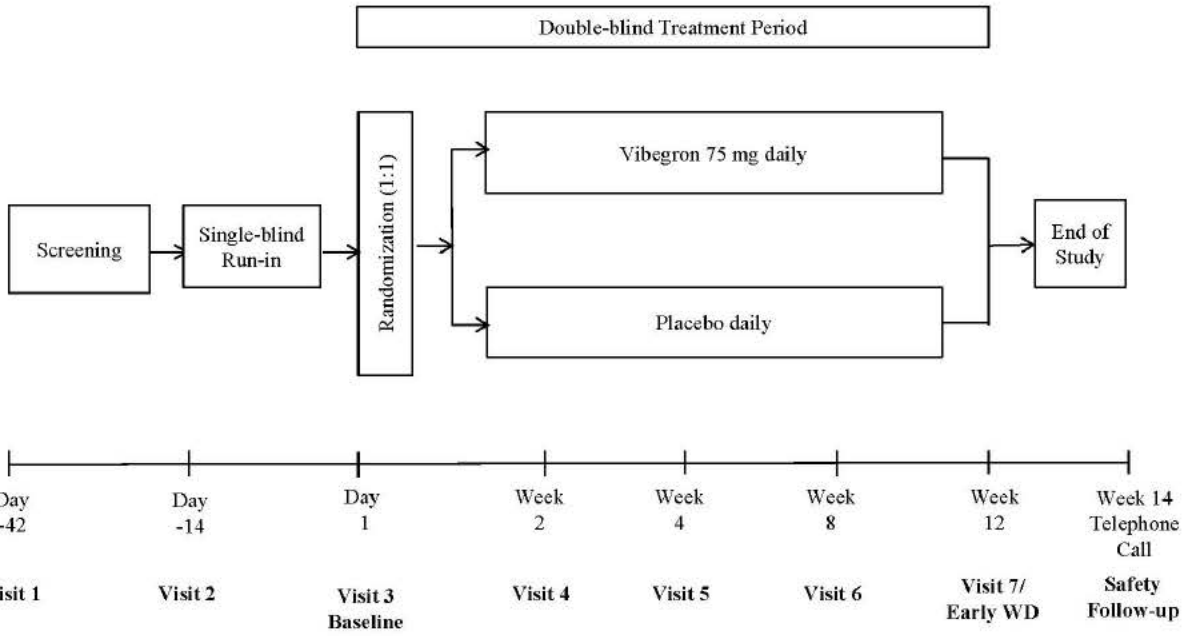
Double-blind Treatment: 1 vibegron (75 mg) or matched placebo tablet daily for up to 12 weeks

Data Safety Monitoring Committee:

A Data Safety Monitoring Board (DSMB) will be retained to assess, on an ongoing basis, all safety aspects of this study, including serious AEs (SAEs), major adverse cardiac events (MACE), adverse events of special interest (AESIs), and all other AEs. The committee will meet to review the safety data at the following 3 times when the (1) first 25% of subjects enrolled complete the Week 4 visit (Visit 5); (2) first 50% of subjects enrolled complete the Week 4 visit (Visit 5); and (3) first 75% of subjects enrolled complete the Week 4 visit (Visit 5). This

committee will be an external independent DSMB that monitors the safety for URO-901-2001. The detailed activities including meeting plans will be described and documented in the DSMB Charter. A separate statistical analysis plan will be prepared for the DSMB.

1.2. Schema



WD = withdrawal

The Week 14 Safety Follow-up telephone call should occur 7 to 14 days after the last dose of study drug (includes window of −7 days from Week 14) only for randomized subjects who complete Week 12 or withdraw from the study early.

1.3. Schedule of Assessments

	Screening	Run-in	Double-blind Treatment					Safety Follow-up	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Telephone Call	
Day/Week	**Day -42 to -15**	**Day -14**	**Baseline Day 1**	**Week 2 (Day 15)**	**Week 4 (Day 29)**	**Week 8 (Day 57)**	**Week 12 or Early WD (Day 85)**	**Week 14 or 14 days after last dose (at the latest)**	**Notes**
Visit Window		**± 4 days**		**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**−7 days**	Safety Follow-up call will occur 7 to 14 days after the last dose of study drug (includes window of −7 days) [a]
Informed consent	X								
Subject entry into IWRS and subject registry	X								
Inclusion and exclusion criteria review	X	X	X						Recheck clinical status before Run-in and randomization
Demographics	X								
Medical history and surgical history	X								Includes current use of illicit drugs, alcohol and caffeine
IBS history	X								Including previous treatments and diets
AE/SAE review	X	X	X	X	X	X	X	X	From informed consent to Safety Follow-up call
Concomitant medication review	X	X	X	X	X	X	X	X	

	Screening	Run-in	Double-blind Treatment					Safety Follow-up	
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Telephone Call**	
Day/Week	**Day -42 to -15**	**Day -14**	**Baseline Day 1**	**Week 2 (Day 15)**	**Week 4 (Day 29)**	**Week 8 (Day 57)**	**Week 12 or Early WD (Day 85)**	**Week 14 or 14 days after last dose (at the latest)**	**Notes**
Visit Window		**± 4 days**		**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**−7 days**	Safety Follow-up call will occur 7 to 14 days after the last dose of study drug (includes window of −7 days) [a]
Vital signs	X	X	X	X	X	X	X		Body temperature, blood pressure (avg of 3 results) and pulse after sitting for 5 min and before blood draw: Visits 1 to 7 Weight: Visits 1, 3, and 7 Height: Visit 1
Brief physical examination	X		X				X		Heart, lungs, abdomen, external genitalia, perianal area, and others as needed
Urine β-hCG pregnancy test	X		X				X		Women of child-bearing potential only; serum test required if urine test positive
Urine drug screen	X	X[c]							Refer to exclusion criterion #29 and Section 6.5 for additional details on possible repeat testing at Visit 2 in the event of an initially positive result at Visit 1.

	Screening	Run-in	Double-blind Treatment					Safety Follow-up	
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Telephone Call**	
Day/Week	**Day -42 to -15**	**Day -14**	**Baseline Day 1**	**Week 2 (Day 15)**	**Week 4 (Day 29)**	**Week 8 (Day 57)**	**Week 12 or Early WD (Day 85)**	**Week 14 or 14 days after last dose (at the latest)**	**Notes**
Visit Window		**± 4 days**		**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**−7 days**	Safety Follow-up call will occur 7 to 14 days after the last dose of study drug (includes window of −7 days) [a]
Laboratory assessments (chemistry, hematology, urine dipstick) [b]	X		X	X	X	X	X		Tests specified in Section 10.2
Serum tissue transglutaminase antibody (IgA)	X								Screening only
12-lead ECG	X								Screening only; supine
Dispense/collect subject diary		X Dispense					X Collect		Bowel Movement Diary will record bowel movement frequency and form, bowel urgency, and recurrent bowel movements; Pain Diary will record worst abdominal pain and use of rescue meds
Dispense Run-in study drug		X							Daily dosing
Administer witnessed dose of study drug		X	X						
Randomization			X						

	Screening	Run-in	Double-blind Treatment					Safety Follow-up	
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Telephone Call**	
Day/Week	**Day -42 to -15**	**Day -14**	**Baseline Day 1**	**Week 2 (Day 15)**	**Week 4 (Day 29)**	**Week 8 (Day 57)**	**Week 12 or Early WD (Day 85)**	**Week 14 or 14 days after last dose (at the latest)**	**Notes**
Visit Window		**± 4 days**		**± 4 days**	**± 4 days**	**± 4 days**	**± 4 days**	**−7 days**	Safety Follow-up call will occur 7 to 14 days after the last dose of study drug (includes window of −7 days) [a]
Dispense new bottle of double-blind study drug for daily dosing			X		X	X			At Visit 4 (Week 2), the Visit 3 (Baseline) bottle will checked for compliance and returned to subject
GIS			X	X	X	X	X		Before vital signs and blood draw
WPAI			X			X	X		Before vital signs and blood draw
IBS-QoL			X			X	X		Before vital signs and blood draw
Additional questions on abdominal pain (see Section 10.8.4)			X	X	X	X	X		Before vital signs and blood draw

AE = adverse event; avg = average; ECG = electrocardiogram; GIS = Global Improvement Scale; IBS = irritable bowel syndrome; IBS-QoL = irritable bowel syndrome quality of life; IWRS = interactive web response system; min = minutes; SAE = serious adverse events; WD = withdrawal; WPAI = Work Productivity and Activity Impairment

[a] Safety Follow-up telephone call will occur only for randomized subjects who complete Week 12 or withdraw from the study early.

[b] A sample for urinalysis and urine culture/sensitivity testing will be sent to the laboratory if the urine dipstick performed at the site suggests a urinary tract infection (ie, positive for the presence of leukocytes, nitrites, or blood cells). In addition, subjects presenting with symptoms of a urinary tract infection at Unscheduled Visits will have a urine dipstick performed, with subsequent urinalysis and culture/sensitivity testing if dipstick suggests urinary tract infection.

[c] For subjects who had a positive urine drug screen at Visit 1 due to a prohibited concomitant medication, the urine drug screen must be repeated at Visit 2 to determine if sufficient washout of the prohibited concomitant medication has occurred and to confirm eligibility. The urine drug screen does not need to be re-tested at Visit 2 if the initial positive result at Visit 1 was due to a permitted concomitant medication based on the clinical judgment of the investigator.

2. Introduction

2.1. Study Rationale

This study will evaluate the efficacy and safety of vibegron, a beta-3 adrenergic receptor (β_3-AR) agonist, in the treatment of pain associated with irritable bowel syndrome (IBS) that is associated with predominantly diarrhea (IBS-D) or has mixed episodes of diarrhea and constipation (IBS-M). The rationale for the study is based on both animal models of functional gastrointestinal disorders and Phase 1 and Phase 2 clinical studies of the β_3-AR agonist solabegron. Animal models have shown that β_3-AR activation can protect against gastric ulcers, inhibit castor-oil induced diarrhea, and reduce observed pain behavior [Vasina, 2008; Cellek, 2007]. The clinical studies of solabegron have shown improvement in pain among women with IBS, with no effect on gut motility in healthy subjects [Grudell, 2008; Kelleher, 2008]. Although this is the first study of vibegron in the setting of IBS, vibegron has been studied in the overactive bladder population (including a completed large Phase 2b dose-ranging study, 2 completed Phase 3 studies in Japan, and 2 ongoing global Phase 3 studies), and all clinical data available to date indicate that vibegron has been well tolerated.

2.2. Background

2.2.1. Irritable Bowel Syndrome

Irritable bowel syndrome is a chronic, functional, bowel disorder associated with changes in the frequency or consistency of stool (ie, diarrhea, constipation, or a combination of both) as well as abdominal pain and distension [Sinagra, 2017]. The etiology of IBS is complex and affects bidirectional communication between the central and the enteric nervous system (ie, gut-brain axis). Altered colonic motility, defects in epithelial and secretory function, immune dysfunction, neurohormonal regulation, stress, and infection have been implicated in the pathogenesis of IBS [Occhipinti, 2012]. The Rome IV criteria classify IBS into 4 distinct subtypes based on predominant stool consistency: IBS with predominantly constipation (IBS-C), IBS with predominantly diarrhea (IBS-D), IBS with mixed episodes of diarrhea and constipation (IBS-M), and IBS with unknown subtype (IBS-U) [Lacy, 2017]. The definitions of diarrhea and constipation correlate with the Bristol Stool Form Scale, with Types 1 and 2 defined as constipation and Types 6 and 7 defined as diarrhea. The Rome IV IBS classification is based on the patient's predominant bowel habit on days with abnormal bowel movement as follows:

- IBS-C: ≥ 25% constipation (Bristol Type 1 or 2) and < 25% diarrhea (Bristol Type 6 or 7).
- IBS-D: ≥ 25% diarrhea (Bristol Type 6 or 7) and < 25% constipation (Bristol Type 1 or 2)
- IBS-M: ≥ 25% constipation (Bristol Type 1 or 2) and ≥ 25% diarrhea (Bristol Type 6 or 7)
- IBS-U: unclassified (insufficient abnormality to meet other criteria)

The Rome IV diagnostic criteria must be met within the most recent 3 months, with symptom onset at least 6 months before diagnosis.

Among functional gastrointestinal disorders, IBS is the most prevalent, affecting approximately 11% of the world's population (range: 1% to 45%, depending on country and criteria) [Lovell, 2012]. Epidemiology studies indicate that gender plays a role in the development of IBS, as women are at a higher risk for the condition than men; however, the predominance of women has been observed only in Western countries (approximately 2:1 to 5:1, depending on the care setting) possibly because of under diagnosis or differences in diet or infection risk factors [Sinagra, 2017]. IBS has a significant impact on quality of life and considerable economic burden to the health care system, with total cost (direct and indirect) estimates of $30 billion in the United States (US) [Lembo, 2007].

Abdominal pain is an important aspect and largely unmet medical need of IBS. Visceral structures are highly sensitive to distension, ischemia, and inflammation, and activation of nociceptors in response to tension or stretching can cause pain in patients with IBS. Colon spasms are common in patients with IBS and are associated with the symptoms of pain and bloating. Patients with IBS may also exhibit visceral hypersensitivity (ie, lowered pain threshold) [Melchior, 2018; Camilleri, 2008; Sabate, 2008]. IBS pain is often refractory to currently available therapeutic options (ie, diet, antispasmodics, antidepressants, laxatives, or antidiarrheals), creating a significant challenge for clinicians and patients trying to manage the disorder [Camilleri, 2017]. In addition, the side effects associated with pharmacotherapies, such as the anticholinergic effects of antispasmodics, may lead to lack of compliance or even discontinuation of treatment [Camilleri 2017; Saha 2014].

2.2.2. Vibegron

Vibegron is a potent, highly selective, orally available, β_3-AR agonist demonstrating > 9000-fold selectivity for activation of β_3-AR over β_2-AR and β_1-AR in cell-based in vitro assays. Nonclinical and clinical studies suggest β_3-AR activation is a novel target for treating pain and gastrointestinal motility in patients with IBS. β_3-ARs are widely expressed and distributed on vascular and non-vascular smooth muscle and enteric neurons in the gastrointestinal tracts of many species, including humans [Cellek, 2007; De Ponti, 1996; Anthony, 1996; Krief, 1993].

Mechanistically, β_3-AR agonists are hypothesized to reduce colon smooth muscle contractions, enteric neuron hyperactivity, and visceral pain by mediating a direct effect on smooth muscle and indirectly by promoting release of somatostatin within the intestine. In isolated circular muscle strips of human colon, activation of β_3-AR induced smooth muscle relaxation [Cellek, 2007; De Ponti, 1999; Bardou, 1998; De Ponti, 1996], which was blocked using β_3-AR antagonists [Schemann, 2010; De Ponti, 1999]. In addition, β_3-AR agonists have been shown to reduce hyperexcitability of human enteric neurons and stimulate release of somatostatin [Schemann, 2010; Cellek, 2007], which inhibits submucosal neuronal excitability and pain in both animal models and humans [Prasoon, 2015; Shi, 2014; Mihara, 1987].

Approximately 2300 subjects (including 1840 with overactive bladder and 460 healthy subjects) have received vibegron in 19 clinical studies. Data from these studies indicate that vibegron has been well tolerated when administered alone or in combination with the following drugs: antimuscarinics (imidafenacin or tolterodine); metoprolol (a representative beta-blocker); or amlodipine (a representative vasodilator). Assessment of safety laboratory parameters and mean vital sign values over time, including heart rate and blood pressure, showed no clinically meaningful differences for any active treatment group relative to placebo or an antimuscarinic comparator. Discontinuation rates due to AEs were low (less than 5%) in all clinical studies. A more detailed description of vibegron, including pharmacology, efficacy, and safety data in overactive bladder, is provided in the most recent version of the Investigator's Brochure.

2.3. Benefit/Risk Assessment

2.3.1. Potential Benefits

Vibegron's novel mechanism of action has the potential to demonstrate significant therapeutic benefit in subjects with IBS pain. Early phase clinical studies of another β_3-AR agonist, solabegron, showed improvement in the pain scores of women with IBS and no effect on gut motility in healthy subjects [Grudell, 2008; Kelleher, 2008].

2.3.2. Potential Risks

To date, in subjects (male or female) with overactive bladder, no adverse reactions specific to vibegron have been identified.

Based on aggregate preclinical, clinical pharmacology, and Phase 2 and 3 studies, AEs of special interest (AESIs) predefined for specific evaluations in vibegron clinical studies are as follows:

- Potential major cardiovascular events
- Hypertension
- AEs suggestive of orthostatic hypotension
- AEs suggestive of cystitis or urinary tract infection
- Elevated AST or ALT lab value requiring that the study drug be temporarily withheld or permanently discontinued

Prespecified definitions of AESIs are provided in Section 8.4.7. More detailed information about the known and expected benefits and risks and reasonably expected AEs of vibegron may be found in the most recent version of the Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the effect of vibegron vs placebo in subjects with abdominal pain due to IBS-D on the API weekly responder rate over 12 weeks	• Proportion of IBS-D subjects who are API weekly responders over 12 weeks – An API Weekly Responder is defined as a subject who experiences a decrease in the weekly average of "worst abdominal pain in the past 24 hours" scores of at least 30% compared with the baseline weekly average
Secondary	
To compare the effect of vibegron vs placebo in subjects with abdominal pain due to IBS-D or IBS-M on patient-reported outcomes	• Proportion of GIS responders at Week 12 for all IBS subjects, including IBS-D and IBS-M subjects
To compare the effect of vibegron vs placebo in subjects with abdominal pain due to IBS-D on the API weekly responder rate over 12 weeks based on different thresholds of improvement	• Proportion of IBS-D subjects who are API weekly responders over 12 weeks – An API Weekly Responder is defined as a subject who experiences a decrease in the weekly average of "worst abdominal pain in the past 24 hours" scores of **at least 40%** compared with the baseline weekly average • Proportion of IBS-D subjects who are API weekly responders over 12 weeks – An API Weekly Responder is defined as a subject who experiences a decrease in the weekly average of "worst abdominal pain in the past 24 hours" scores of **at least 50%** compared with the baseline weekly average
To compare the effect of vibegron vs placebo in subjects with abdominal pain due to IBS-D or IBS-M on safety endpoints	• AEs, clinical laboratory values, vital signs

Objectives	Endpoints
Other/Exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

Objectives	Endpoints
[redacted]	

AE(s) = adverse event(s); API = Abdominal Pain Intensity; GIS = Global Improvement Scale; IBS = irritable bowel syndrome; IBS-D = irritable bowel syndrome with predominantly diarrhea; IBS-M = irritable bowel syndrome with mixed episodes of diarrhea and constipation; PRO = patient-reported outcomes; IBS-QoL = irritable bowel syndrome Quality of Life; WPAI = Work Productivity and Activity Impairment

4. Study Design

4.1. Overall Design

This study is a Phase 2 randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of vibegron in women with IBS-D or IBS-M. Subjects who meet all eligibility criteria will be randomized in a 1:1 ratio to receive either vibegron 75 mg or matched placebo. Randomization will be stratified by baseline abdominal pain intensity score (< 6 vs ≥ 6 on a 0 to 10 numeric rating scale [NRS]) and IBS subtype (IBS-D vs IBS-M). Enrollment for subjects with IBS-M will be capped at 50% of the total subject population (ie, up to 50% of the study population will be subjects with IBS-M). Stratification will be performed via central randomization across the study (not per site).

A Data Safety Monitoring Board (DSMB) will be retained to assess, on an ongoing basis, all safety aspects of this study, including SAEs, major adverse cardiac events (MACE), adverse events of special interest (AESIs), and all other AEs. The committee will meet to review the safety data at the following 3 times when the (1) first 25% of subjects enrolled complete the Week 4 visit (Visit 5); (2) first 50% of subjects enrolled complete the Week 4 visit (Visit 5); and (3) first 75% of subjects enrolled complete the Week 4 visit (Visit 5).

The study consists of a Screening Period (1 to 5 weeks), a single-blind Run-in Period (2 weeks), a randomized, double-blind Treatment Period (12 weeks), and a Safety Follow-up telephone call (2 weeks). The Safety Follow-up telephone call will occur 14 days (with a window of -7 days) after the subject's last dose of study drug (ie, at Week 14 for subjects who complete the Week 12 Visit, or 2 weeks after the last dose of study drug for randomized subjects who discontinue treatment early) (see Schedule of Assessments, Section 1.3). Additionally, Unscheduled Visits may be arranged for subjects with study-related safety concerns as needed.

Approximately 200 subjects will be enrolled at approximately 40 sites in the US to achieve approximately 90 evaluable IBS-D subjects (45 per treatment group). Enrollment will be competitive. The sample size justification is provided in Section 9.2.

4.1.1. Clinical Hypotheses

The primary objective will be to estimate the treatment effect of vibegron relative to placebo with respect to improvement in IBS-related abdominal pain in IBS-D subjects. There is no formal statistical hypothesis. Nominal p-values from comparisons to placebo may be provided for descriptive purposes.

4.2. Scientific Rationale for Study Design

A single-blind, placebo Run-in Period will be used to assess placebo response and to ensure that subjects have adequate experience with dosing compliance and completing the diaries. The double-blind Treatment Period will include a placebo arm to accurately demonstrate and measure

the efficacy of vibegron. Subjects with IBS-D or IBS-M were chosen as the study population because the abdominal pain due to colonic contractions in these subjects is an unmet medical need that may be addressed by vibegron's ability to relax smooth muscle contractions, as demonstrated in the overactive bladder population. The study population is limited to women because data from the Phase 2 clinical study of the β_3-AR agonist solabegron have shown improvement in IBS pain among women [Kelleher, 2008].

4.3. Justification for Dose

This study is a proof-of-concept study that will evaluate the effect of vibegron in subjects with IBS-D or IBS-M. The dose of vibegron for this study (75 mg once daily) is the same dose that was evaluated in the recent Phase 3 program for subjects with overactive bladder. The evidence to support this dose comes from the following data:

- Several Phase 2 and Phase 3 clinical studies with vibegron at doses up to 100 mg (including 75 mg) have demonstrated that it is generally safe, well tolerated, and efficacious in subjects with overactive bladder over 52 weeks of treatment:
    - Vibegron 75 mg (2 Phase 3 studies): Studies 3003 and 3004
    - Vibegron 50 mg and 100 mg (2 Phase 3 studies and 1 Phase 2b study): Studies 301, 302, and 008
- Study 008 demonstrated dose-dependent significant efficacy over placebo across multiple clinical endpoints in overactive bladder, with the maximal effect generally estimated at doses between 50 and 100 mg
- Compared with placebo, no clinically relevant differences in heart rate or blood pressure were observed for vibegron (50 and 100 mg once daily) in the overactive bladder population
- Vibegron 75 mg administered once daily is expected to capture approximately 90% of the efficacy of 100 mg daily; the mean trough concentration for vibegron 75 mg at steady-state is 40 ng/mL, which is several fold above the β_3 half-maximal effective concentration of 1.7 nM (0.76 ng/mL)

The dose of vibegron used in this IBS study (75 mg once daily) is expected to have a similar safety profile to that observed with the same dose in the overactive bladder population.

4.4. End of Study Definition

The end of the study is defined as the date that the last subject completes both the Week 12 Visit and Week 14 Safety Follow-up Telephone Call Visit, discontinues from the study, or is lost to follow-up.

A subject is considered to have completed the study if she completes 12 weeks of double-blind treatment at the Week 12 Visit.

5. Study Population

The study is being conducted in women with IBS-D or IBS-M, which is representative of the subject population to which the results will be generalized. Specific inclusion and exclusion criteria are specified below. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Subjects may be rescreened **once** to meet inclusion criteria (see Section 5.4).

5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply at Visit 1 (Screening), unless otherwise noted:

1. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form, including agreeing to patient registry verification.
2. Female, 18 to 70 years of age, inclusive
3. Body weight ≥ 50 kg; body mass index < 45
4. Diagnosis of IBS-D or IBS-M according to the Rome IV criteria:
    - Recurrent abdominal pain, on average at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:
        - Related to defecation
        - Associated with a change in frequency of stool
        - Associated with a change in form (appearance) of stool
    - Diagnostic criteria must be fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.
    - Subtyping performed by the predominant stool pattern present in a subject:
        - IBS-D: loose, mushy, or watery stools (Bristol Type 6 or 7) for > 25% of bowel movements and hard or lumpy stools (Bristol Type 1 or 2) for < 25% of bowel movements
        - IBS-M: hard or lumpy stools (Bristol Type 1 or 2) for > 25% of bowel movements and loose, mushy, or watery stools (Bristol Type 6 or 7) for > 25% of bowel movements
5. Has completed a colonoscopy according to the American Gastroenterological Association criteria (if necessary), with no clinically significant findings in the last 5 years
6. Willing and able, as assessed by the Investigator, to follow study instructions, including completing the subject diaries and quality of life questionnaires and attending all study visits
7. Willing and able to maintain regular diet for the duration of the study
8. Has no clinically significant findings on a physical examination or clinical laboratory tests that could interfere with study participation or confound study assessments, in the

opinion of the Investigator. Serum tissue transglutaminase antibody (IgA) must be negative. Fecal calprotectin testing is optional and should only be considered if there is a strong suspicion that the subject has IBD (eg, family history in a 1st degree relative, other genetic factors, etc.) or other organic disease, according to the clinical judgement of the investigator.

9. Women of childbearing potential must agree to use one of the contraception methods listed in Section 10.6.1
10. Agrees not to participate in another clinical trial while participating in this study
11. At **Baseline (Visit 3)**,
    - Must continue to meet all inclusion criteria
    - During any 5 days in the 7 days immediately prior to Baseline (Visit 3), as reported in the subject's daily pain diary:
      - Subject must have a weekly average of "worst abdominal pain in the past 24 hours" score of ≥ 3.0 on a 0- to 10-point NRS (see Section 10.9 for NRS)

5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply at Visit 1 (Screening), unless otherwise noted:

1. Diagnosis of IBS-C or IBS-U per Rome IV criteria
2. History of chronic idiopathic constipation or functional constipation
3. Current or history (in the past year) of substance or alcohol abuse, alcoholism, alcohol addiction, or drinks > 3 alcoholic beverages per day (one drink defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of distilled spirits)
4. History of clinically relevant liver disease or severe hepatic impairment (Child-Pugh Class C)
5. Pre-existing condition that has altered normal gastrointestinal anatomy (eg, prior bariatric surgery or gastric banding, solitary rectal ulcer syndrome)
6. History of or suspected mechanical gastrointestinal obstruction or current symptoms suggestive of gastrointestinal obstruction or infection
7. Diverticulitis within prior 3 months
8. Structural abnormality of the gastrointestinal tract or a disease or condition that can affect gastrointestinal motility
9. History of a gastrointestinal motility disorder other than IBS (eg, gastroparesis, intestinal pseudo-obstruction, achalasia, Parkinson's disease, multiple sclerosis, spinal cord injury)
10. Severe constipation or sequelae from constipation
11. Active duodenal or gastric ulcer
12. History of solitary rectal ulcer syndrome

13. Prior history of a gastrointestinal malignancy, inflammatory bowel disease, celiac disease
14. History of colitis (ischemic, lymphocytic, collagenous or radiation-induced) or hepatic and/or renal function that could interfere with the absorption, metabolism and/or excretion of the study drug (eg, carcinoid syndrome, amyloidosis)
15. Uncomplicated appendectomy within the past 3 months; subjects who had an appendectomy that was associated with any related complications or sequelae are eligible if the procedure was performed at least 6 months prior and all complications/sequelae have resolved
16. Planned gastrointestinal or abdominal surgery within the next 6 months
17. Co-existing gastroesophageal reflux disease or functional dyspepsia with symptoms predominant to IBS symptoms
18. Symptoms or diagnosis of a medical condition other than IBS that may contribute to abdominal pain (eg, interstitial cystitis; fibromyalgia currently being treated with pregabalin or gabapentin; and endometriosis with uncontrolled abdominal pain)
19. History of pancreatitis, structural diseases of the pancreas (including known or suspected pancreatic duct obstruction), known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction; acute, symptomatic cholecystitis or symptomatic cholelithiasis within the last 6 months is also exclusionary
20. Lactose intolerance not controlled by lactose-free diet
21. History or evidence of symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting surgery, percutaneous transluminal coronary angioplasty, cerebrovascular accident, transient ischemic attack, or any clinically significant cardiac disease
22. Clinically significant electrocardiogram (ECG) abnormality that, in the opinion of the Investigator, exposes the subject to risk by participating in the study.
23. Uncontrolled hypertension (sitting systolic blood pressure ≥ 180 mmHg and/or sitting diastolic blood pressure ≥ 100 mmHg) or resting heart rate (by pulse) > 100 beats per minute
24. Systolic blood pressure ≥ 160 mmHg but < 180 mmHg is excluded unless deemed by the Investigator as safe to proceed in this study and agreed to by the Sponsor's designated Medical Monitor; must be on stable hypertension medication for at least 3 months prior to entering Run-in (Visit 2)
25. Concurrent malignancy or history of any malignancy (within the last 5 years), except non-metastatic basal or squamous cell carcinoma of the skin that has been treated successfully
26. Uncontrolled diabetes mellitus defined by a hemoglobin A1C level > 8%
27. Significant psychiatric or psychologic disorder that would preclude meaningful participation in the study (eg, bipolar disorders or schizophrenia; however, treated

depression on a stable regimen [eg SNRI, SSRI] is allowed) in the opinion of the Investigator

28. Presence of any unexplained alarm symptoms (eg, anemia, gastrointestinal bleeding, unintentional weight loss, suspected malignancy)
29. Use of any prohibited medications, such as eluxadoline, for which a subject cannot complete the appropriate washout period (see Section 6.5.1). Positive urine drug screen at Visit 1 is exclusionary except for the following situations:
    - Subjects who have a positive urine drug screen at Visit 1 due to a prohibited concomitant medication that can be washed out, the urine drug screen must be repeated at Visit 2 to determine if sufficient washout of the prohibited concomitant medication has occurred and to confirm eligibility
    - If the initial positive result at Visit 1 was due to a permitted concomitant medication (see Section 6.5.2), based on the clinical judgment of the investigator, a subject is still eligible and the urine drug screen would not need to be re-tested at Visit 2
30. Dose change for any medications requiring a stable dose (see Section 6.5.2) prior to the Screening Visit or plans to initiate or change the dosing of any of these medications during the study
31. Currently participating in or has participated in a study with an investigational compound or device or procedure within 28 days prior to screening
32. Currently participating in or has participated in a study with vibegron
33. ALT or AST > 2.0 times upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome)
34. Lipase > 2 x ULN
35. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2
36. Women who are pregnant, nursing, or planning a pregnancy during the study
37. History of sensitivity to any of the study drugs, or components thereof, or a history of drug or other allergy that, in the opinion of the Investigator, contraindicates study participation
38. At **Baseline (Visit 3)**, noncompliant with dosing during the 2-week Run-in Period (taking < 80% or > 120% of study medication)
39. Clinically significant medical or surgical history or any condition that could interfere with study participation or confound the assessments in the opinion of the study Investigator

5.3. Lifestyle Considerations

Subjects are expected to maintain their pre-study diet for the duration of the study. Alcoholic drinks must be limited to ≤ 3 per day (one drink is defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of distilled spirits).

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) that occurred within the Screening Period.

Individuals who do not meet the criteria for participation in the study (screen failures prior to initiation of run-in study medication) may be rescreened **once** upon consultation with, and approval by, the Sponsor's designated Medical Monitor, Sponsor, or its designee. Subjects who initiate Run-in study drug dosing may not be rescreened. Rescreened subjects will be assigned a new subject number, and both subject numbers will be linked to the subject, and a new informed consent with the new subject number should be signed. Screening assessments specified in Section 1.3 should be repeated if subjects are rescreened.

6. Study Drug

6.1. Study Drugs Administered

Study Drug Name	Vibegron	Matched Placebo
Dosage Formulation	tablet	tablet
Identity of Formulation	75 mg	placebo
Route of Administration	oral	oral
Dosing Instructions	once daily	once daily
Packaging and Labeling	Study drug will be provided in HDPE bottles with child resistant caps. Each bottle will contain 32 tablets and will be labeled as required per country requirement.	Study drug will be provided in HDPE bottles with child resistant caps. Each bottle will contain 32 tablets and will be labeled as required per country requirement.
Manufacturer	Patheon, Cincinnati, Ohio, US	Patheon, Cincinnati, Ohio, US
Number and Timing of Drugs	Treatment Period: 1 tablet daily	Run-in Period: 1 tablet daily Treatment Period: 1 tablet daily

HDPE = high density polyethylene

The study drug will be supplied in bottles each containing 32 tablets (4-week supply) and labeled with the protocol number, bottle number, lot number, expiration date, study drug name (vibegron 75 mg or placebo tablets), number of tablets, directions for use, storage information, warning language (*Keep Out of Reach of Children. For Clinical Trial Use Only. To be used by qualified Investigators only. Caution: New Drug—Limited by United States Law to Investigational Use.*), and the US Sponsor name and address. Immediately before dispensing the study drug, the Investigator (or appropriately trained designee) will write the subject number, visit number. and the dispense date on the detachable panel of the label, which also includes the protocol number, bottle number and lot number.

6.1.1. Run-in Medications and Administration

During the single-blind Run-in Period, all subjects will take 1 tablet of study drug (ie, placebo) once daily for 2 weeks. All subjects will take their first dose of study drug at the study site as a witnessed dose. The date and time of the study drug dosing will be recorded. The Investigator will be aware that the study drug is placebo, but the subject will not know either the identity of the treatment or that entry into the double-blind Treatment Period is dependent on compliance with dosing in the Run-in Period. The matched placebo will be identical in appearance to the study drug administered during double-blind treatment.

6.1.2. Treatment Period Medications and Administration

During the double-blind Treatment Period, subjects will take 1 tablet of study drug (vibegron or matched placebo) once daily for up to 12 weeks. The appearance of the vibegron and placebo tablets will be identical. All subjects will take their first dose of study drug at the study site as a witnessed dose. The date and time of the study drug dosing will be recorded.

6.2. Preparation/Handling/Storage/Accountability

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of study drug must be recorded by an authorized person at the study site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

The Investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study. These records will be monitored throughout the study.

For all sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

6.3. Measures to Minimize Bias: Randomization and Blinding

Single-blind (Run-in only) and double-blind (Treatment Period) techniques will be used. Vibegron and its matched placebo will be packaged identically so that the treatment blind is maintained. The subject, Investigator, and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects will be unaware of the treatment group assignments during the double-blind Treatment Period. Subjects will be centrally assigned to randomized study drug using an interactive web response system (IWRS) and the randomization schedule generated by the Sponsor or designee. Before the screening is initiated at each site, login information and directions for the IWRS will be provided.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's study drug assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor or designee prior to unblinding a subject's study drug assignment unless this could delay emergency treatment of the subject. If a subject's study drug assignment is unblinded, the Sponsor or designee must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

At the end of the study, the official, final database will be frozen and unblinded after medical/scientific review has been performed, and data have been declared final and complete. The Sponsor will be granted access to the unblinded database in order to analyze the data. A clinical study report will be prepared after all subjects complete the study.

6.4. Study Drug Compliance

Study drug compliance will be closely monitored by counting the number of tablets dispensed and returned. Before dispensing new study drug at applicable visits, study site personnel will make every effort to collect all unused study drug and empty bottles.

The study site will keep an accurate drug disposition record that specifies the amount of study drug administered to each subject and the date of administration.

6.5. Concomitant Therapy

The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the subject's electronic case report form (eCRF) at each visit, along with the reason the medication is taken, the dates of administration, and the dose.

6.5.1. Prohibited Drugs and Washout Before the Study

Table 6-1 provides a list of specific restrictions for concomitant therapy use during the study, with any necessary washout periods described (see Section 6.5.2 for permitted medications requiring a stable dose prior to study entry and Table 6-1 for the list of prohibited medications and washout periods). For subjects who had a positive urine drug screen at Visit 1 due to a prohibited concomitant medication, the urine drug screen must be repeated at Visit 2 to determine if sufficient washout of the prohibited concomitant medication has occurred and to confirm eligibility. The urine drug screen does not need to be re-tested at Visit 2 if the initial positive result at Visit 1 was due to a permitted concomitant medication based on the clinical judgment of the Investigator.

If there is a clinical indication for any therapy that is specifically prohibited during the study, discontinuation from study drug may be required. The Investigator should discuss any questions regarding this with the Sponsor's designated Medical Monitor. The final decision on any supportive therapy rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject on study treatment requires the mutual agreement of the Investigator and the Sponsor's designated Medical Monitor.

Consult the Sponsor's designated Medical Monitor if there is any uncertainty regarding subject use of a particular drug or drug class.

Table 6-1 Prohibited Medications

Class	Examples	Washout Period
Mu-opioid receptor agonist	eluxadoline	1 month prior to Run-in (Visit 2)
Opiates and narcotic pain-relievers	morphine, codeine, paregoric, opium, propoxyphene, fentanyl, methadone	14 days prior to Run-in (Visit 2)
Beta agonists	mirabegron, dobutamine, isoprenaline, albuterol (systemic only)	14 days prior to Run-in (Visit 2)
Musculoskeletal drugs	baclofen, cyclobenzaprine, methocarbamol, metaxalone	14 days prior to Run-in (Visit 2)
Previous use of antibiotics to treat IBS	rifaximin, neomycin	90 days prior to Run-in (Visit 2)
Antibiotics[a]	amoxicillin, doxycycline, cephalexin, ciprofloxacin	14 days prior to Run-in (Visit 2)
Psychoactive drugs used to treat IBS	cannabis products (including systemic cannabidiol [CBD])	14 days prior to Run-in (Visit 2)
CNS stimulants	cocaine, amphetamines	14 days prior to Run-in (Visit 2)
Barbiturates	Phenobarbital[b], secobarbital	14 days prior to Run-in (Visit 2)
NMDA receptor agonist	phencyclidine	14 days prior to Run-in (Visit 2)

CNS = central nervous system; IBS = irritable bowel syndrome; NMDA = N-methyl-D-aspartate
[a] Antibiotics are permitted during the Treatment Period as needed.
[b] Unless prescribed and at stable doses as anticonvulsant for documented epilepsy.

6.5.2. Permitted Drugs

Medications listed in Table 6-2 are permitted as long as the dose has been stable for the specified time period.

Table 6-2 Medications Permitted at Stable Doses

Class	Examples	Stable Dose Period
Anticonvulsants for subjects with documented epilepsy	Carbamazepine, gabapentin, pregabalin, topiramate	6 months prior to Run-in (Visit 2)
Antidepressants	Tricyclic antidepressants, trazodone, SNRIs (eg, duloxetine), SSRIs	3 months prior to Run-in (Visit 2)
Antihypertensives	Diuretics, ACE inhibitors, calcium channel blockers, angiotensin receptor blockers, beta blockers, alpha agonists	3 months prior to Run-in (Visit 2)
Injectable and standard therapy for acute, episodic or chronic migraine unless prohibited (Section 6.5.1)	Botulinum toxin A injections, erenumab or other CGRP antagonists if approved, triptans	1 month prior to Run-in (Visit 2)
Antispasmodics/smooth muscle relaxants and peppermint oil	Otilonium, pinaverium, hyoscyamine, dicyclomine, peppermint oil, butylscopolamine	1 month prior to Run-in (Visit 2)

ACE = angiotensin-converting enzyme; CGRP = calcitonin gene-related peptide; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI= Selective Serotonin reuptake inhibitor

Medications for the treatment of allergies, chronic medical conditions, and acute migraines are permitted with the exception of prohibited pain medications (see Section 6.5.1). As needed, the use of benzodiazepines for anxiety is permitted.

With the exception of the agents specified in Table 6-1 and the medications requiring stable doses prior to study entry (Table 6-2), any other concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the Investigator. If the permissibility of a specific medication/drug is in question, please contact the Sponsor's designated Medical Monitor. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded in the eCRF. Allowed rescue medication for pain, constipation, and diarrhea are listed in Section 6.5.3.

6.5.3. Rescue Medicine

Rescue medications should only be used starting at Day 1 (Visit 3) or after. The following rescue medications may be used:

For pain

- Equivalent of ibuprofen 400 mg twice daily or less
- Low-dose acetaminophen 500 mg three times daily or less
- Low-dose aspirin (≤ 325 mg daily)

For constipation (not thought to affect IBS pain)

- Polyethylene glycol
- Bisacodyl (no more than one 5-mg dose weekly)

For diarrhea (not thought to affect IBS pain)

- Loperamide (up to 4 mg four times daily)

Rescue medications will not be provided by the Sponsor.

Use of rescue medication will be collected on the daily diary (ie, subjects will respond to prompts asking if any rescue medication was taken for abdominal pain or stool symptoms). During the subsequent subject visit, the details of the rescue medication will be collected for inclusion on the concomitant medication eCRF page, as needed.

6.6. Dose Modification

No dose modification of study drug is permitted. Study drug should be withheld for liver test abnormalities as described in Section 8.4.7.1.

6.7. Drug after the End of the Study

No further study drug will be administered to subjects who complete the study.

7. Discontinuation of Study Drug and Subject Discontinuation/Withdrawal

A premature discontinuation will occur if a subject who signs the informed consent form (ICF) and is randomized ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

7.1. Discontinuation of Study Drug

Subjects who discontinue study drug post-randomization will complete the Week 12/Early Withdrawal assessments specified in the Schedule of Assessments (Section 1.3). Reasons for discontinuation from double-blind study drug treatment and the study include the following:

- Adverse event (AE)
- Lack of efficacy
- Noncompliance
- Withdrawal of consent
- Lost to follow-up
- Physician decision
- Protocol deviation
- Pregnancy
- Death
- Other

Discontinuation of study drug for abnormal liver function should be considered by the Investigator when a subject meets all of the conditions outlined in Section 8.4.7.2 for Hy's law or if the Investigator believes that it is in the best interest of the subject (reason for discontinuation will be AE). Reporting and follow-up requirements for pregnancy are provided in Section 8.4.5 and Section 10.6.2.

For subjects who are not randomized into the 12-week double-blind treatment period and, therefore, are either screen failures or run-in failures, the End of Study eCRF should be completed (refer to eCRF completion guidelines for additional information).

7.2. Subject Discontinuation/Withdrawal from the Study

- Subjects who discontinue post-randomization study drug will also withdraw from the study.
- A subject may choose to withdraw from the study at any time at her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If a subject withdraws consent for disclosure of future information, the Sponsor or designee may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, she may request destruction of any blood or urine samples taken and not tested, and the Investigator must document this in the site study records.
- Subjects who withdraw from the study will not be replaced (enrollment accounts for a predetermined dropout rate).
- The Week 12/Early Withdrawal assessments will be completed, if possible, when a subject withdraws or is withdrawn from the study (see Schedule of Assessments in Section 1.3).

7.3. Lost to Follow-up

Should a subject fail to attend a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up", including at least three documented attempts to contact the subject (ie, phone, email, or certified letter). Efforts to establish the possible reason for discontinuation should be documented.

7.4. Early Study Termination

The Sponsor reserves the right to terminate the study at any time. The study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study overall or at a particular study site may be stopped due to insufficient compliance with the protocol, Good Clinical Practice or other applicable regulatory requirements; procedure-related problems; or the number of discontinuations for administrative reasons is too high.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the Schedule of Assessments (Section 1.3). A detailed listing of study assessments by visit is provided in Section 10.7.

- Protocol waivers or exemptions are not allowed; however, subjects who fail to meet eligibility criteria may be rescreened once, as appropriate. Any notable protocol deviations should be noted and raised to the Sponsor's or designee's attention.
- Immediate safety concerns should be discussed with the Sponsor's designated Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.
- Note that patient-reported outcome (PRO) assessments will be completed prior to vital signs, and vital signs will be taken prior to blood draws.

8.1. Baseline Procedures

8.1.1. Informed Consent

Documented consent must be obtained from each potential subject prior to participating in any study procedures according to the process described in Section 10.1.3.

8.1.2. Assignment of Subject Number

All subjects who sign the ICF will be assigned a unique subject number by IWRS. This number will be used to identify the subject throughout the study. Subjects who are rescreened will be assigned a new subject number. If a new number is assigned, the subject will be linked to both subject numbers.

8.1.3. Screening

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will be reviewed by the Investigator or qualified designee at Screening, the start of the Run-in Period, and the start of the double-blind Treatment Period.

Subjects who fail to meet entry criteria may be rescreened **once** upon consultation with, and approval by, the Sponsor's designated Medical Monitor, Sponsor, or designee (See Section 8.1.2 regarding subject number).

The Screening Period may also be used for washout of prohibited medications (see Section 6.5.1).

8.1.4. Medical History

A medical history will be obtained by the Investigator or qualified designee. Medical history will include all chronic and ongoing conditions, regardless of year diagnosed; surgical history; substance abuse history; and IBS history (eg, Rome subtype, date of diagnosis, prior treatment). A history of previous diets for IBS and their perceived effectiveness will also be collected. All events occurring after the subject signs the ICF will be recorded as AEs.

8.1.5. Demographics

Demographic data collection will include sex, age, race, and ethnicity.

8.1.6. Prior and Concomitant Medications

Prior IBS medications and ongoing (concomitant) medications will be recorded beginning at the signing of the ICF and continuing until the Safety Follow-up call.

8.2. Efficacy Assessments

Efficacy assessments will be collected as outlined in the Schedule of Assessments (Section 1.3).

Assessment	Timing	Measurement
Abdominal Pain Intensity (API)	Daily during Run-in and double-blind Treatment Period	• 0- to 10-point numeric rating scale: – 0 = no pain – 10 = worst possible pain Subjects will record worst abdominal pain on evening Pain Diary in response to daily prompt
PRO Questionnaires	At Baseline and specified visits during double-blind Treatment Period before vital signs and blood draw	• GIS • WPAI • IBS-QoL • Additional abdominal pain questions
[redacted]		

eCRF = electronic case report form; GIS = Global Improvement Scale; IBS-QoL = IBS quality of life assessment; PRO = patient-reported outcomes; WPAI = Work Productivity and Activity Impairment

8.2.1. Symptom Diaries

Subjects will complete 2 diaries daily, a Bowel Movement Diary and a Pain Diary. The Bowel Movement Diary will be event-driven (ie, subjects will record events as they occur) and will capture bowel movement frequency and form, bowel urgency, and recurrent bowel movements. The Pain Diary will prompt subjects each evening to answer a question regarding worst abdominal pain for the past 24 hours using the 0- to 10-point NRS to rate pain and to capture use of rescue medications.

Subjects will receive the diaries and be trained on their use at the start of the Run-in Period (Visit 2). At subsequent visits, subjects will be re-instructed or retrained as needed. Subjects

must be able to complete the diaries to be eligible for the study. Further details on training and the use of the diaries are provided in a separate manual.

8.2.2. Patient-reported Outcomes

Subjects will complete questionnaires at the site at the start of each required study visit (before vital signs and blood draws) to assess subject-perceived symptom relief and health-related quality of life. The PRO questionnaires are provided in Section □.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the Schedule of Assessments (Section 1.3). Immediate safety concerns should be discussed with the Sponsor's designated Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.

8.3.1. Physical Examinations

Brief physical examinations will include examination of the heart, lungs, abdomen, visual examination of the external genitalia and perianal area, and any other areas as needed. In addition, any organ system in which a previous abnormality was noted at Baseline or a subject has a complaint or AE will be examined.

8.3.2. Vital Signs

Vital signs, including blood pressure, pulse, body temperature, weight, and height, will be assessed at the timepoints specified in the Schedule of Assessments (Section 1.3) and Section 10.7 as follows:

- Blood pressure and pulse will be measured after the subject has been resting in a seated position for 5 minutes, after PRO assessments and before any blood draws.
- Blood pressure measurements will be taken on the same arm and by the same site staff throughout the study, if possible.
- Sitting systolic and diastolic blood pressures will be determined by averaging 3 replicate measurements obtained 1 to 2 minutes apart. The average of the 3 measurements will be used for eligibility and safety assessments.
- The same method for assessing temperature should be used at all visits for a particular subject.
- Body weight will be measured with subjects in street clothing with jacket/coat and shoes removed, using the same scale throughout the study, if possible.
- Standing height will be measured without shoes, at Screening only.

8.3.3. Electrocardiograms

At Screening only, a 12-lead ECG will be performed in the supine position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECGs will be read by trained personnel at the study site.

8.3.4. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments, as defined in Section 10.2 and including urine pregnancy test and drug screen, must be conducted in accordance with the laboratory manual and the Schedule of Assessments (Section 1.3). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The clinical significance of test results will be evaluated as follows:

- At Screening, the Investigator or physician sub-investigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and subjects with abnormalities judged to be clinically significant will be excluded from the study.
- The Investigator or physician sub-investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significant during participation in the study or within 14 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor's designated Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor's designated Medical Monitor notified.
  - If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the eCRF.

8.4. Adverse Events and Serious Adverse Events

The definitions of an AE and SAE can be found in Section 10.3.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue the study drug or the study (see Section 7).

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from the signing of the ICF through 14 days after the last dose of study drug. AEs will be collected at the timepoints specified in the Schedule of Assessments (Section 1.3), and as observed or reported spontaneously by study subjects.

Medical occurrences that begin before the start of double-blind study drug, but after obtaining informed consent, will be recorded in the AE section of the eCRF.

All SAEs (including serious AESIs) will be recorded and reported on the eCRF within **24 hours** of the study site personnel's knowledge of the event, as indicated in Section 8.4.4. Marking the event as "serious" will automatically send required notifications for Sponsor or designee review. The Investigator will also submit any updated SAE data within 24 hours of receipt of the information. Nonserious AESIs will be reported on the eCRF within **72 hours** of the site's knowledge of the information.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs will be followed until the Week 14 Safety Follow-up telephone call (14 days [with a −7-day window] after the last dose of study drug). All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). If a subject dies during participation in the study or

within 14 days of the last dose of study drug, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed eCRF. As noted above, the Investigator will submit any updated SAE data within 24 hours of receipt of the information.

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification of an SAE by the Investigator to the Sponsor or designee is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study drug under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB) or Independent Ethics Committee (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor or designee will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

If any subject becomes pregnant during the study (from signing the ICF through 14 days after the last dose of study drug), the site must discontinue the subject from study drug immediately and have the subject return for an Early Withdrawal Visit (Week 12 Visit assessments). The Investigator must inform the subject of the right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the subject (see Section 6.3 for unblinding information). The study team will remain blinded to the subject's treatment assignment.

In the case of a pregnant subject, if she agrees, the Investigator should notify the subject's primary care physician of the pregnancy and provide details of the subject's participation in the study and treatment (blinded or unblinded, as applicable).

A pregnancy is to be reported to the Sponsor's designated Medical Monitor **within 24 hours of awareness** by the study site personnel using the contact information on the Study Contacts Page and the dedicated pregnancy reporting form. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, neonatal data, etc. should be included in this information, as available.

The Investigator will follow the medical status of the mother, the pregnancy, as well as the outcome of the infant at birth, and will report the outcome to the Sponsor or designee.

If the pregnant subject experiences an SAE during pregnancy, or the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (ie, report the event on the AE eCRF within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs. In addition, any infant death or congenital anomaly occurring after study completion that the Investigator suspects is related to the in-utero exposure to the study drug should also be reported. Refer to Section 10.6.2 for additional information regarding collection of pregnancy data.

8.4.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

No disease-related events or outcomes are excluded from AE reporting. Any worsening of diarrhea or constipation and any new onset of constipation should be collected as AEs.

8.4.7. Adverse Events of Special Interest

Selected nonserious and serious AEs will be reported as AESIs. The events must be reported on the AE eCRF within 24 hours of the study site personnel's knowledge of the event. AESIs that also meet the definition of an SAE must be reported as described in Section 10.3.

Adverse events of clinical interest for this study include:

- Potential major cardiac and cerebrovascular events, including death (or any event with fatal outcome), myocardial infarction, cerebrovascular accident, hospitalization for unstable angina or chest pain, hospitalization for heart failure, and coronary revascularization/angioplasty/stent
- Hypertension, defined as follows:
  - [redacted]

- [redacted]
- AEs consistent with orthostatic hypotension as confirmed by orthostatic vital signs
- AEs suggestive of cystitis or urinary tract infection (UTI)
- [redacted]
- Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) lab value requiring that study drug be temporarily withheld or permanently discontinued (see Sections 8.4.7.1 and 8.4.7.2). To date, no concern regarding drug-induced liver toxicity has been identified; however, the Sponsor is monitoring laboratory data for a potential safety signal, consistent with Food and Drug Administration (FDA) guidance [FDA Guidance, 2009].

Serious AESIs and elevated liver enzymes or bilirubin requiring withholding of study drug must be reported within 24 hours of the study site personnel's knowledge of the event by marking the appropriate box on the AE eCRF and assigning the most appropriate category. Additional information should be provided as directed in the eCRF Completion Guidelines. AESIs that also meet the definition of an SAE must be reported as an SAE, as described in Section 8.4.4. Nonserious AESIs should be reported within 72 hours of the site personnel's knowledge, using the AE eCRF.

8.4.7.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Elevated liver enzymes or bilirubin sufficient to require withholding study medication must be reported **within 24 hours of the study site personnel's knowledge of the event** using AESI -specific eCRFs/forms/worksheets provided for the study.

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA Guidance, 2009].

If **any** of the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status), and the event reported as an SAE:

- ALT or AST > 8 x upper limit of normal (ULN)
- ALT or AST > 5 x ULN and persists for more than 2 weeks
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The Investigator and Sponsor's designated Medical Monitor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug-induced.

8.4.7.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug should be discontinued permanently if **all** of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

- Total bilirubin increases to > 2 x ULN or INR > 1.5 **and**
- AST or ALT increases to ≥ 3 x ULN **and**
- Alkaline phosphatase value does not reach 2 x ULN **and**
- No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to, the following:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus)
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
  - Alcoholic hepatitis
  - Non-alcoholic steatohepatitis

- Autoimmune hepatitis

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug should be withheld or permanently discontinued as appropriate for the safety of the subject, following consultation with the Sponsor's designated Medical Monitor.

8.4.8. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study drug as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong subject (ie, not administered to the intended subject)

Medication errors include occurrences of overdose and underdose of the study drug.

Overdose: Unintentional administration of a quantity of the study drug given per administration or per day that is above the maximum recommended dose according to the protocol. This also takes into account cumulative effects due to overdose (see Section 8.5 for treatment and reporting of overdose). For this study, any dose of vibegron or placebo > 2 tablets within a 24-hour window is an overdose. There is no known antidote for an overdose.

Underdose: No underdose is defined for this study.

8.5. Treatment of Overdose

In the event of an overdose (> 2 tablets of study drug within 24 hours), the Investigator or treating physician should:

- Contact the Sponsor's designated Medical Monitor immediately
- Closely monitor the subject for any AEs, SAEs, and laboratory abnormalities
- Report all overdose events within 24 hours of awareness by the study site, using the Overdose eCRF, whether or not the overdose is associated with an AE
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor's designated Medical Monitor based on the clinical evaluation of the subject.

9. Statistical Considerations

This section contains a brief summary of the statistical analyses for this study; full details will be provided in the Statistical Analysis Plan (SAP).

The randomized allocation schedule will be generated by the Sponsor or designee and implemented by the vendor of the study. Stratification will be performed across the study (not per site). The statistical analysis of the data obtained from this study will be the responsibility of the Sponsor or designee. At the end of the study, the official, final database will be frozen and unblinded after medical/scientific review has been performed, and data have been declared final and complete. The SAP will be approved prior to data being unblinded.

A subject is considered enrolled in the study at randomization.

9.1. Statistical Hypotheses

The primary objective will be to estimate the treatment effect of vibegron relative to placebo with respect to improvement in IBS-related abdominal pain in IBS-D subjects. There is no formal statistical hypothesis. Nominal p-values from comparisons to placebo may be provided for descriptive purposes. An improvement in the primary endpoint is defined as a subject who experiences a decrease in the weekly average of "worst abdominal pain in the past 24 hours" scores of at least 30% compared with the baseline weekly average.

9.2. Sample Size Determination

In total, approximately 200 subjects will be randomized in a 1:1 ratio to receive 1 of the following study drugs:

- Vibegron 75 mg (N = 100)
- Placebo (N = 100)

At most, 50% of randomized subjects (approximately 100 subjects total [50 per treatment arm]) will have IBS-M; and at least 50% of randomized subjects (approximately 100 subjects total [50 per treatment arm]) will have IBS-D, and the IBS-D subgroup will be used for the primary endpoint analysis.

Assuming a total of 10% of subjects will discontinue prior to Week 12 (for any reason), there will be a minimum of approximately 90 evaluable IBS-D subjects (45 in the vibegron arm and 45 in the placebo arm) at the end of Week 12. The study has approximately 60% power to detect a between-group treatment difference of 20% in proportion of abdominal pain responders at a 2 -sided test at the $\alpha = 0.10$ level assuming a responder rate of 51% versus 31% for vibegron and placebo, respectively. The assumptions were based on results from a solabegron study female subgroup analysis [Kelleher, 2008].

9.3. Populations for Analyses

The analysis populations will consist of subjects as defined below:

- The Screened Analysis Set includes all subjects who are screened for the study. This population is used primarily for subject accounting purposes and will generally not be used for summary or analysis.
- The Randomized Set includes all subjects who are randomized to receive study drug regardless of whether they take a dose.
- The Safety Analysis Set includes all subjects who receive at least one dose of study drug. Subjects will be classified according to the treatment they actually receive.
- The Full Analysis Set (FAS) includes all randomized IBS-D and IBS-M subjects who took at least one dose of double-blind study drug and had a baseline diary assessment and at least 1 post -randomization diary entry. Subjects will be analyzed according to randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the Intent -to-Treat principle. The Full Analysis Set for IBS-D (FAS-D) and Full Analysis Set for IBS-M (FAS-M) are each a subset of FAS and consists of IBS-D and IBS-M subjects, respectively. The FAS-D will serve as the primary population for the primary analysis of efficacy data in this study.
- The Per-Protocol Set for IBS-D excludes subjects from the FAS-D due to important deviations from the protocol that may substantially affect the result of the primary efficacy endpoint (ie, Major Protocol Deviations associated with efficacy). The Per -Protocol Set will serve as the supportive population for the analysis of efficacy data in this study. Other Per-Protocol Sets may be defined.

9.4. Statistical Analyses

Endpoints that will be evaluated for within- and/or between-treatment differences are provided below. The descriptions of the endpoints and timepoints at which they are measured are described in Section 3 and the Schedule of Assessments (Section 1.3).

In general, continuous variables will be summarized by treatment to indicate the population sample size (N), number of subjects with available data (n), arithmetic mean, standard deviation (SD), median, first and third quartile, minimum and maximum values. Categorical variables will be summarized by N, n, number of subjects in each category and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. Tables summarizing demographics and other baseline characteristics will also include a column for all subjects combined.

9.4.1. Demographic and Other Baseline Characteristics

All demographic data such as age, sex, race, ethnicity and baseline characteristic data will be summarized by treatment group for the Full Analysis Set. Subject disposition will be summarized using the Screened Analysis Set.

Descriptions of medical history findings will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 (or later). Medical history may be summarized in the descending order of overall frequency, by System Organ Class (SOC) and Preferred Term (PT).

Prior and concomitant medications will be coded using the latest version of World Health Organization Drug Dictionary. The number and percentage of subjects receiving prior or concomitant medications will be summarized by treatment group.

9.4.2. Efficacy Analyses

Statistical analysis of efficacy endpoints will be for descriptive purposes only. Nominal p-values will be based on statistical tests will be 2-sided hypothesis tests performed at the 10% level of significance for main effects. All confidence intervals will be 2-sided 90% confidence intervals, unless stated otherwise. When summarizing diary data by visit, including weekly response endpoints, only the data from the 7 days prior to the subject's clinic visit will be included.

9.4.2.1. Primary Efficacy Analysis

Response efficacy endpoints from Week 1 through Week 12 will be analyzed using the Cochran -Mantel-Haenszel risk difference estimate. The estimated difference in the proportion of responders and 90% confidence interval for the difference will be calculated using the Cochran -Mantel-Haenszel risk difference estimate stratified by baseline abdominal pain (< 6 vs ≥ 6) with weights proposed by Greenland and Robins.

For the analysis of other continuous endpoints (eg, change from baseline at Week 12), a mixed model for repeated measures with restricted maximum likelihood estimation will be used by incorporating on treatment- values at all time points. The analysis model for the efficacy endpoint will include terms for treatment, visit, baseline score, and interaction of visit by treatment. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment for denominator degrees of freedom will be used with restricted (or residual) maximum likelihood to make statistical inference.

Further details will be provided in the SAP.

9.4.2.2. PRO Analyses

Details of PRO analyses will be provided in the SAP.

9.4.2.3. Exploratory Efficacy Analyses

Details of exploratory efficacy analyses will be provided in the SAP.

9.4.2.4. Multiplicity Adjustment

No formal multiplicity adjustment will be performed. All efficacy analyses will be considered descriptive. Ninety-percent confidence intervals will be provided for each treatment group and nominal p-values from comparisons to placebo may be provided for descriptive purposes. The nominal p-values will be tested using a hierarchical testing strategy using 2-sided tests with significant level $\alpha = 0.10$. Nominal p-values will be provided for all secondary efficacy analyses as a measure of the strength of the association between the endpoint and the treatment effect rather than formal tests of hypotheses.

9.4.3. Safety Analyses

The safety analysis will be performed using the Safety Analysis Set and will be fully defined in the SAP. The safety parameters will include AEs and clinical laboratory and vital sign parameters. For each safety parameter of the clinical laboratory and vital sign parameters, the last non--missing safety assessment before the first dose of double-blind study drug will be used as the baseline for all analyses of that safety parameter.

9.4.3.1. Adverse Events

An AE will be considered a treatment-emergent AE (TEAE) if:

- The AE began on or after the date of the first dose of study drug; or
- The AE was present before the date of the first dose of study drug, but increased in severity or became serious on or after the date of the first dose of study drug

An AE that occurs more than 14 days after the last dose of study drug will not be counted as a TEAE.

An AE will be considered a treatment-emergent SAE (TESAE) if it is a TEAE that additionally meets any SAE criteria.

AEs will be coded using MedDRA version 21.1 (or later). An overall summary table of AEs by treatment group will be presented with number and percentage of subjects. The incidence of all TEAEs by primary SOC and PT will be prepared for all TEAEs, serious TEAEs, treatment -related TEAEs, treatment-related serious TEAEs, TEAEs leading to discontinuation from study drug, AESIs, and all TEAEs by maximum intensity. All AEs will be listed, with a flag designating AEs that are treatment emergent.

9.4.3.2. Clinical Laboratory Assessments

All continuous safety laboratory parameters will be summarized descriptively by absolute value at each visit by treatment group, together with the corresponding changes from baseline. Central laboratory reference ranges will be used to identify abnormalities with low, normal or high.

9.4.3.3. Vital Signs

Descriptive statistics of observed values and change from baseline for vital signs will be presented for each treatment group by visit.

9.5. Interim Analyses

9.6. Data Safety Monitoring Board

One external independent DSMB will be formed for the study URO-901-2001. The detailed activities including meeting and analysis plan will be described and documented in the DSMB Charter and the DSMB SAP, respectively.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH/ISO Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor or designee with sufficient, accurate financial information as requested to allow the Sponsor or designee to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier. Any subject records or datasets that are transferred to the Sponsor or designee will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. If a subject is rescreened and assigned a new subject number, both subject numbers for that individual will be linked.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor or designee in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor or designee, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Not applicable.

10.1.6. Posting Clinical Study Data

Clinical study information will be posted on external registries and websites (eg, US National Institutes of Health's website www.ClinicalTrials.gov).

10.1.7. Data Quality Assurance

- All subject data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Management of clinical data will be performed in accordance with applicable Sponsor-approved standards and data cleaning procedures to ensure the integrity of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Study Site

All clinical study documentation must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The Investigator must notify the Sponsor before destroying any clinical study records.

The study site and the record retainer should take measures in such a way that these records are not lost or abandoned during the designated period of preservation and that they are presented upon request.

Institutional Review Board, Independent Ethics Committee, Research Ethics Board (IRB/IEC/REB)

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and any other relevant materials, including accompanying material to be provided to the subject (eg, advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IRB/IEC/REB. Approval from the IRB/IEC/REB must be obtained before starting the study and should be documented in a letter to the Investigator specifying the following:

- Protocol number
- Protocol version
- Protocol date
- Documents reviewed

- Date on which the committee met and granted the approval

Any amendments to the protocol will require IRB/IEC/REB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC/REB's annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC/REB
- Notifying the IRB/IEC/REB of SAEs or other significant safety findings as required by procedures established by the IRB/IEC/REB.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must be available during the site monitor's visit.
- The required source documents are:
    - Subject identification (name, date of birth, sex)
    - Documentation that the subject meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria)
    - Participation in the study (including study number)
    - Study discussed and date of informed consent
    - Dates of all visits
    - Documentation that protocol-specific procedures were performed
    - Results of efficacy parameters, as required by the protocol
    - Start and end date (including dose regimen) of study treatment (drug dispensing and return should be documented as well)
    - Record of all AEs and other safety parameters (start and end date, and causality and intensity as assigned by the Investigator)
    - Concomitant medication (including start and end date)
    - Date of study completion and reason for early discontinuation, if applicable

10.1.9. Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC/REB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study drug development

10.1.10. Publication Policy

- The Sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple Investigators and sites and Sponsor or designee personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the Sponsor.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

10.1.11. Compliance with Protocol

The Investigator is responsible for compliance with the protocol at the investigational site. A representative of the Sponsor will make frequent contact with the Investigator and his/her research staff and will conduct regular monitoring visits at the site to review subject and study drug accountability records for compliance with the protocol. Protocol deviations will be discussed with the Investigator upon identification. The use of the data collected for the subject will be discussed to determine if the data are to be included in the analysis. The Investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC/REB according to the IRB/IEC/REB's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 will be performed by the laboratory chosen by the Sponsor or the Sponsor's designee. Subjects do not need to fast prior to laboratory testing. Refer to the Laboratory Manual for information on where testing should be performed (site, local laboratory, central laboratory).

A urine dipstick will be performed at the study site at scheduled visits as noted in the Schedule of Assessments (Section 1.3) and when a subject presents with symptoms of a urinary tract infection at Unscheduled Visits. If the urine dipstick is positive for leukocytes, nitrites, or blood cells, a urinalysis and culture/sensitivity testing will be performed.

A urine pregnancy test will be performed at the site for all women of childbearing potential. If the urine pregnancy test is positive, a serum pregnancy test will be performed.

Table 10-1 Clinical Laboratory Tests

Hematology	**Chemistry**	**Urine Dipstick/ Urinalysis[a]**	**Other**
Hematocrit	Albumin	Blood	Serum β-hCG[b]
Hemoglobin	Alkaline phosphatase	Glucose	Urine drug screen
Platelet count	ALT	Protein	Fecal calprotectin[c,d]
WBC (total and differential)	AST	Specific gravity	Serum tissue transglutaminase antibody (IgA)[d]
RBC	Bicarbonate	Microscopic exam (RBCs, WBCs, epithelial cells and bacteria)	Coagulation (INR/PT/APTT)[g]
	Calcium	pH	
	Chloride	Color	
	Creatinine[e]	Urine pregnancy test (β-hCG)[b]	
	Follicle-stimulating hormone		

Hematology	**Chemistry**	**Urine Dipstick/ Urinalysis[a]**	**Other**
	Glucose (fasting or non-fasting)		
	Lipase		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin[f]		
	Blood urea nitrogen		
	Total cholesterol		

APTT = activated partial thromboplastin time; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = β–human chorionic gonadotropin; INR = international normalized ratio; PT = prothrombin time; RBC = red blood cell count; WBC = white blood cell count

[a] A sample for urinalysis and urine culture/sensitivity testing will be sent to the laboratory only if the urine dipstick performed at the site tests positive for the presence of leukocytes, nitrites, or blood cells.

[b] Urine β-hCG will be tested for women of childbearing potential only. If urine β-hCG is positive, a serum β-hCG must be performed.

[c] Optional at Screening only.

[d] Performed at Screening only per inclusion criterion #8.

[e] Estimated glomerular filtration rate will be calculated and reported by the central lab.

[f] If total bilirubin is elevated above the upper limit of normal.

[g] Only upon request from Principal Investigator (if ALT, AST and bilirubin are increased).

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug. **AE of Special Interest** An AESI (serious or nonserious) is one of scientific and medical concern specific to the Sponsor's study drug or program, which warrants ongoing monitoring and rapid communication by the Investigator to the Sponsor or designee. Such an event might warrant further investigation in order to characterize and understand it. See Section 8.4.7 for AESIs defined for this study.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study drug administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. For this study, report all overdose events within 24 hours of awareness by the study site, using the Overdose eCRF, whether or not the overdose is associated with an AE. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE. Any worsening of diarrhea or constipation and any new onset of constipation in IBS-D subjects should be collected as AEs.

Events NOT Meeting the AE Definition
• Abnormal screening laboratory values, including fecal calprotectin, C-reactive protein, etc. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE. • The disease/disorder being studied or expected signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy) the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term *life-threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been admitted to the hospital or kept in the Emergency Room for ≥ 24 hours for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent activities of daily living but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such medically significant events include invasive or malignant cancers, intensive treatment with a drug in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AEs and SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE or SAE information in the eCRF page.
- All SAEs (including serious AESIs) must be **reported in the eCRF within 24 hours of the study site personnel's knowledge of the event**, regardless of the Investigator assessment of the relationship of the event to study drug.
  - The event term, start date, severity, and initial causality assessment must be entered in the AE eCRF page and the event must be marked as "Serious". This will activate additional assessment fields including "action taken with study drug", "seriousness criteria", and "brief description" which should be completed as soon as information is available. Marking the event as "serious" will automatically send required notifications for Sponsor or designee review.
  - The initial SAE report should include:
    - The date of the report
    - A description of the SAE (event term, seriousness of the event, date of onset, intensity)
    - Causal relationship to the study drug
  - A discharge summary should be provided for all hospitalizations. If the subject died, the report should include the cause of death as the event term (with death as the outcome) and whether the event leading to death was related to study drug, as well as the autopsy findings, if available
- Nonserious AESIs should be reported on the eCRF within 72 hours of knowledge of the information.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor or designee in lieu of completion of the AE or SAE eCRF.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

1/MILD	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
2/MODERATE	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/SEVERE OR MEDICALLY SIGNIFICANT	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/LIFE-THREATENING	Life threatening consequences; urgent intervention indicated
5/DEATH	Death related to adverse event

An event is defined as *serious* when it meets at least one of the predefined criteria as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE or SAE.

A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.

The Investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in his/her assessment.

For each AE or SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE to the Sponsor or designee.**

The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE Reporting
All SAEs must be **reported in the eCRF within 24 hours of the study site personnel's knowledge of the event**, regardless of the Investigator assessment of the relationship of the event to study drug. Marking the event as "Serious" will activate additional assessment fields.

10.4. Appendix 4: Abbreviations

Abbreviation	Definition
β_3-AR	beta-3 adrenergic receptor
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
API	abdominal pain intensity
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GIS	Global Improvement Scale
HRT	hormonal replacement therapy
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with predominantly constipation
IBS-D	irritable bowel syndrome with predominantly diarrhea
IBS-M	irritable bowel syndrome with mixed episodes of diarrhea and constipation
IBS-QoL	irritable bowel syndrome quality of life

IBS-U	irritable bowel syndrome with unknown subtype
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	interactive web response system
MACE	Major Adverse Cardiac Events
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numeric rating scale
OAB	Overactive bladder
PRO	patient-reported outcomes
PT	preferred term
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
WPAI	Work Productivity and Activity Impairment

10.5. Appendix 5: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vibegron Administered Orally for 12 Weeks to Women with Irritable Bowel Syndrome
	Clinical Study Sponsor	Urovant Sciences GmbH
	Trial Phase Classification	Phase 2
	Trial Indication	IBS pain
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	21 weeks
	Planned Country of Investigational Sites	US
	Planned Number of Subjects	Approximately 200
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Diagnosis Group	IBS-D, IBS-M
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	70
	Sex of Subjects	Female
	Stable Disease Minimum Duration	3 months

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	Vibegron
	Drug Type	Drug
	Pharmacological Class of Invest. Therapy	Beta-3 adrenergic receptor agonist
	Dose per Administration	75 mg vibegron (or placebo)
	Dose Units	1 tablet
	Dosing Frequency	Once daily
	Route of Administration	Oral
	Current Therapy or Treatment	Diet, antispasmodics, antidepressants, laxatives, antidiarrheals
	Added on to Existing Treatments	Add on to stable doses of antidepressants, anticonvulsants (for epilepsy), diet
	Control Type	Placebo
	Comparative Treatment Name	--
Trial design	Study Type	Randomized, controlled, double-blind
	Drug Model	Parallel
	Planned Number of Arms	2
	Trial is Randomized	Yes
	Randomization Quotient	0.5
	Trial Blinding Schema	Double blind
	Stratification Factor	Baseline abdominal pain intensity (< 6 vs ≥ 6) and IBS subtype (IBS-D vs IBS-M)
	Adaptive Design	No
	Study Stop Rules	Unacceptable risk/benefit ratio; noncompliance with protocol, GCP, other regulatory requirements; procedure-related issues; unacceptable number of discontinuations for administrative reasons; Sponsor decision

FDA = Food and Drug Administration; GCP = Good Clinical Practice; IBS = irritable bowel syndrome; IBS-D = irritable bowel syndrome with predominantly diarrhea; IBS-M = irritable bowel syndrome with mixed episodes of diarrhea and constipation; US = United States

10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Women in the following categories are not considered women of childbearing potential:

- Premenopausal woman with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.
- Postmenopausal woman
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Women on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.6.1. Contraception Guidance

Women of childbearing potential must agree to use (or have their male partner use) a highly effective contraception method, unless any of the following apply:

- Has reached natural menopause, defined as at least 12 months of spontaneous amenorrhea without an alternative medical cause;
- Is permanently sterile, following hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

Highly effective methods of contraception include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)

- Bilateral tubal occlusion (including ligation and blockage methods such as Essure™ at least 6 months prior to the initial Screening Visit [subjects with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram])
- Sexual partner(s) who was documented to be vasectomized at least 6 months prior to the Screening Visit
- Sexual abstinence from heterosexual intercourse

Subjects will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm when they sign an ICF that they understand the requirements for avoidance of pregnancy during the course of the study.

These methods of contraception are only effective when used consistently, correctly, and in accordance with the product label. The Investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

10.6.2. Pregnancy Testing and Reporting

10.6.2.1. Pregnancy Testing

Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test at Screening, Baseline (Visit 3, prior to dosing), and at Week 12 or Early Withdrawal. A serum β-human chorionic gonadotropin test must be performed if the urine test is positive.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

10.6.2.2. Reporting Pregnancy

The Investigator will collect pregnancy information on any subject who becomes pregnant while participating in this study. Information will be recorded on the dedicated pregnancy reporting form and submitted to the Sponsor or designee within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. A spontaneous or elective abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported using the eCRF as described in

Section 10.3. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any subject who becomes pregnant while participating in the study will discontinue study drug and be withdrawn from the study.

10.7. Appendix 7: Study Schedule Supplement

10.7.1. Screening, Visit 1 (between Day -42 and Day -15)

- Obtain Informed Consent
- Enter subject into IWRS and subject registry
- Assess inclusion/exclusion criteria
- Collect demographic data
- Collect medical and surgical history data including use of illicit drugs, alcohol, and caffeine
- Collect IBS history including previous treatments and diets
- Collect concomitant medications
- Begin recording AEs/SAEs after signing ICF
- Record vital signs (blood pressure [average of 3 results]; record each reading in the source document), body temperature, pulse, weight, and height
- Perform brief physical examination (heart, lungs, abdomen, external genitalia, perianal area, and any other areas as needed)
- Perform urine pregnancy test on women of child-bearing potential; if positive, perform serum test
- Perform urine drug screen
- Perform laboratory assessments, including urine dipstick
- Perform 12-lead ECG

10.7.2. Run-in, Visit 2 (Day -14)

- Assess inclusion/exclusion criteria
- Review concomitant medications
- Record blood pressure (average of 3 results; record each reading in the source document), body temperature, and pulse
- Urine drug screen to be repeated for subjects who had a positive urine drug screen at Visit 1 if due to a prohibited concomitant medication. The urine drug screen does not need to be re-tested at Visit 2 if the initial positive result at Visit 1 was due to a permitted concomitant medication based on the clinical judgment of the investigator.
- Dispense study drug for single-blind Run-in Period
- Administer witnessed dose of study drug
- Review AEs/SAEs
- Dispense subject diary

10.7.3. Baseline, Visit 3 (Day 1)

- Assess inclusion/exclusion criteria
- Review concomitant medications
- Administer questionnaires (GIS, WPAI, IBS-QoL, and additional abdominal pain questions)
- Record blood pressure (average of 3 results; record each reading in the source document), body temperature, pulse, and weight
- Perform brief physical examination (heart, lungs, abdomen, external genitalia, perianal area, and any other areas as needed)
- Perform urine pregnancy test; if positive, perform serum test (subject may not begin double-blind treatment if serum pregnancy test is positive)
- Perform laboratory assessments, including urine dipstick
- Obtain subject randomization assignment
- Dispense double-blind study drug
- Administer witnessed dose of study drug
- Review AEs/SAEs

10.7.4. Double-blind Treatment Period Week 2 (± 4 days), Visit 4

- Administer questionnaires (GIS and additional abdominal pain questions)
- Review AEs/SAEs
- Review concomitant medications, including use of rescue medication from diary
- Record blood pressure (average of 3 results; record each reading in the source document), body temperature, and pulse
- Perform laboratory assessments, including urine dipstick
- Review remaining double-blind study drug from Baseline (Visit 3) for compliance and return to subject

10.7.5. Double-blind Treatment Period Week 4 (± 4 days), Visit 5

- Administer questionnaire (GIS and additional abdominal pain questions)
- Review AEs/SAEs
- Review concomitant medications, including use of rescue medication from diary
- Record blood pressure (average of 3 results; record each reading in the source document), body temperature, and pulse
- Perform laboratory assessments, including urine dipstick
- Dispense double-blind study drug

10.7.6. Double-blind Treatment Period Week 8 (± 4 days), Visit 6

- Administer questionnaires (GIS, WPAI, and IBS-QoL, and additional abdominal pain questions)
- Review AEs/SAEs
- Review concomitant medications, including use of rescue medication from diary
- Record blood pressure (average of 3 results; record each reading in the source document), body temperature, and pulse
- Perform laboratory assessments, including urine dipstick
- Dispense double-blind study drug

10.7.7. Double-blind Treatment Period Week 12 (± 4 days [Visit 7]), or Early Withdrawal

- Administer questionnaires (GIS, WPAI, IBS-QoL, and additional abdominal pain questions)
- Collect subject diary
- Review AEs/SAEs
- Review concomitant medications, including use of rescue medication from diary
- Record blood pressure (average of 3 results; record each reading in the source document), body temperature, pulse, and weight
- Perform brief physical examination (heart, lungs, abdomen, external genitalia, perianal area, and any other areas as needed)
- Perform urine pregnancy test on women of child-bearing potential; if positive, perform serum pregnancy test
- Perform laboratory assessments, including urine dipstick
- Collect double-blind study drug

10.7.8. Safety Follow-up, Telephone Call; Week 14 (7 to 14 days after last dose of study drug; includes window of −7 days from Week 14)

- Contact subject to review AEs and concomitant medications; only for randomized subjects who complete Week 12 or withdraw from the study early.

10.8. Appendix 8: Patient-Reported Outcomes Questionnaires

10.8.1. Global Improvement Scale

Global improvement assessment asks subjects to evaluate their current IBS status by asking the following question: How would you rate your IBS signs or symptoms overall over the past 7 days?

1) significantly relieved
2) moderately relieved
3) slightly relieved
4) unchanged
5) slightly worse
6) moderately worse
7) significantly worse

A responder is defined as a subject who answered that their symptoms were either moderately relieved or significantly relieved [Gordon, 2003; Lembo, 2001].

10.8.2. Irritable Bowel Syndrome - Quality of Life Measure (IBS – QoL)

1. I feel helpless because of my bowel problems.
   ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

2. I am embarrassed by the smell caused by my bowel problems.
   ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

3. I am bothered by how much time I spend on the toilet.
   ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

4. I feel vulnerable to other illnesses because of my bowel problems.
   ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

5. I feel fat because of my bowel problems.
   ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

6. I feel like I'm losing control of my life because of my bowel problems.
   ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

7. I feel like life is less enjoyable because of my bowel problems.
   ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

8. I feel uncomfortable when I talk about my bowel problems.
   ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

9. I feel depressed about my bowel problems.
   ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

10. I feel isolated from others because of my bowel problems.
    ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

11. I have to watch the amount of food that I eat because of my bowel problems.
    ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

12. Because of my bowel problems, sexual activity is difficult for me.
    ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

13. I feel angry that I have bowel problems.
    ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

14. I feel like I irritate others because of my bowel problems.
    ❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

15. I worry that my bowel problems will get worse.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

16. I feel irritable because of my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

17. I worry that people think I exaggerate my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

18. I feel I get less done because of my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

19. I have to avoid stressful situations because of my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

20. My bowel problems reduce my sexual desire.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

21. My bowel problems limit what I can wear.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

22. I have to avoid strenuous activity because of my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

23. I have to watch the kind of food I eat because of my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

24. Because of my bowel problems, I have difficulty being around people I do not know well.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

25. I feel sluggish because of my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

26. I feel unclean because of my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

27. Long trips are difficult for me because of my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

28. I feel frustrated that I cannot eat when I want because of my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

29. It is important to be near a toilet because of my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

30. My life revolves around my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

31. I worry about losing control of my bowels.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

32. I feel that I won't be able to have a bowel movement.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

33. My bowel problems are affecting my closest relationships.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ A great deal

34. I feel that no one understands my bowel problems.
❒ Not at all ❒ Slightly ❒ Moderately ❒ Quite a bit ❒ Extremely

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10.8.3. Work Productivity and Activity Impairment

Work Productivity and Activity Impairment Questionnaire:
General Health V2.0 (WPAI:GH)

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

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

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

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

   _____HOURS

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

   _____HOURS

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

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

5. During the past seven days, how much did your PROBLEM affect your productivity while you were working?

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

   Consider only how much PROBLEM affected productivity while you were working.

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

   CIRCLE A NUMBER

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

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

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

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

CIRCLE A NUMBER

WPAI:GH V2.0 (US English)

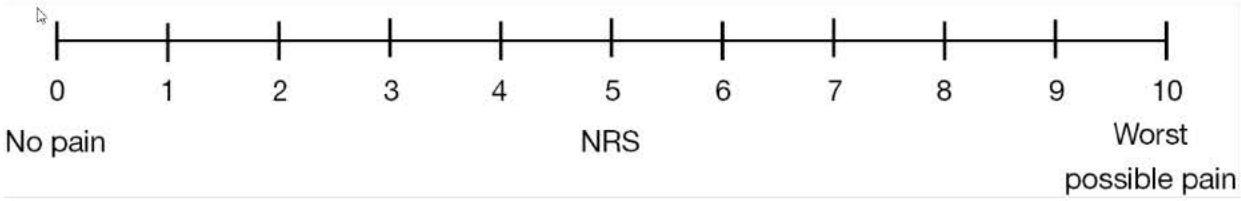
[Reilly, 1993]

10.8.4. Additional Questions on Abdominal Pain

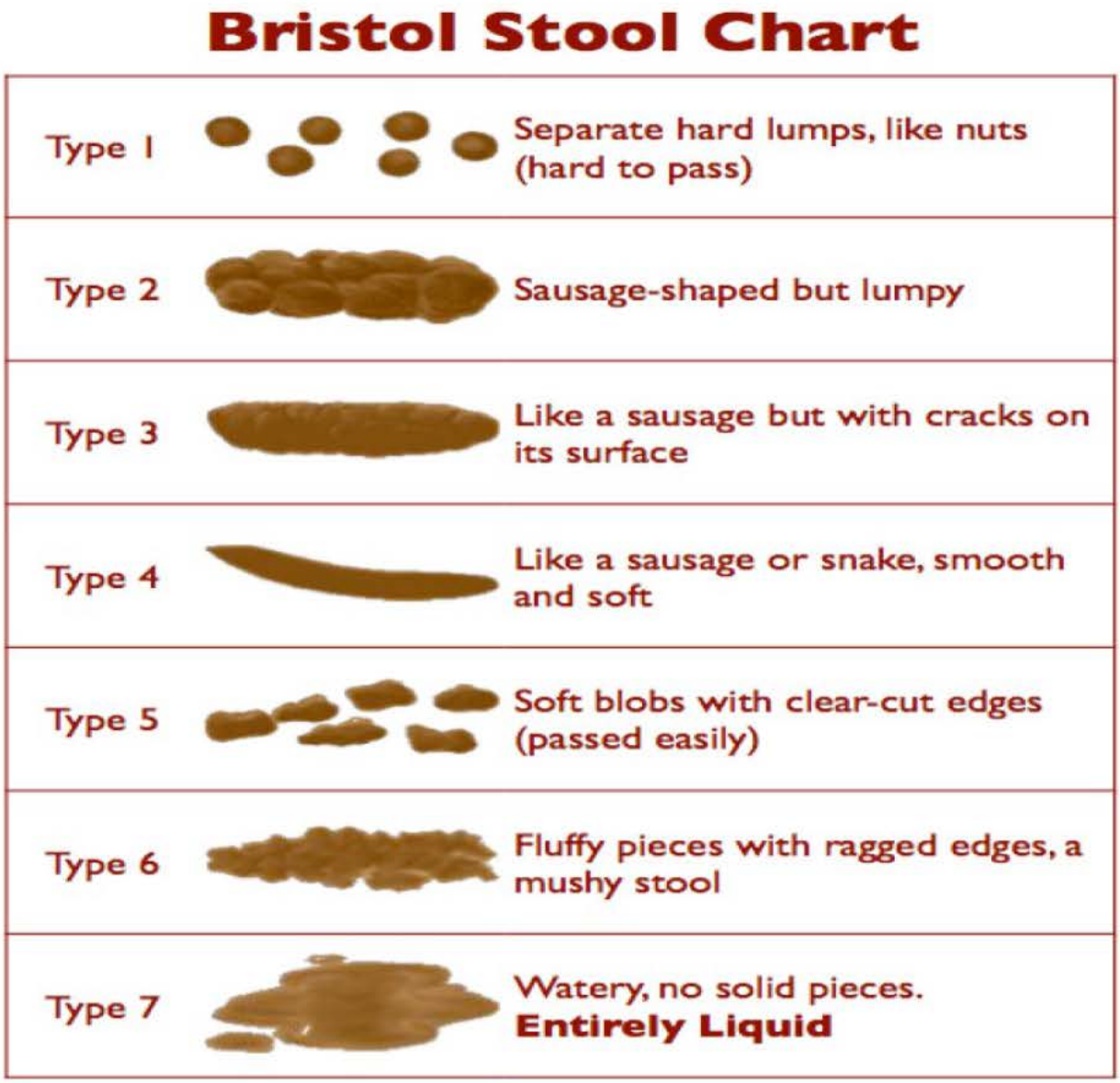
1. Did you experience abdominal pain within 1 hour of eating? Yes/No
2. Did you experience abdominal pain associated with a bowel movement? Yes/No

10.9. Appendix 9: 0- to 10-Point Numeric Rating Scale for Abdominal Pain

On a scale of 0 to 10 where "0" is equal to no pain and "10" is worst possible pain, how would you rate your IBS-related abdominal pain at its worst in the past 24 hours?



10.10. Appendix 10: Bristol Stool Chart



[Lewis, 1997]

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