16.1 Study Information

16.1.1 Protocol and protocol amendments

The following documents are included:

- Final protocol, dated 18 Aug 2015

CLINICAL STUDY PROTOCOL

Protocol No. TEN-01-301

A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study with a 4-Week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C)

18 August 2015
Edition No. 1

SPONSOR:

Ardelyx, Inc.
34175 Ardenwood Blvd.
Fremont, CA USA 94555
[redacted]

PROTOCOL SUMMARY

Study Title	A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study with a 4-Week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C)
Sponsor	Ardelyx, Inc.
Study Phase	3
Treatment Groups	2 treatment groups; ~600 subjects total; ~300/group with a ratio of 1:1 Tenapanor:placebo
No. of Sites	100-120
Dose Form and Frequency	Tablet(s), placebo matched Twice daily (BID)
Doses	Placebo, and tenapanor 50 mg BID (total daily doses; placebo, and 100 mg)
Methodology	This is a 12-week, multi-center, randomized, double-blind, placebo controlled study with a 4-week randomized withdrawal (RW) period to evaluate tenapanor 50 mg BID in subjects with IBS-C (Rome III criteria). A 2:1 screen to randomization ratio is expected.
Duration	For each subject, the entire study will last for a total of 18 weeks; including 16 weeks of treatment, preceded by a 2 week screening period.
2-Week Screening Period	At the beginning of the 2-week screening period (Day -14), the following will be performed: Subjects will provide written consent and be fully assessed for eligibility into the study. The assessments will include: inclusion/exclusion criteria, medical histories (including details about co-morbid disorders), physical exam, vital signs, ECG, and clinical laboratory tests. During the 2-week screening period, subjects will self-report, on a daily basis, information about the status of their IBS-C symptoms via an electronic diary. At the end of the screening period, prior to the subject returning for Visit 2 (randomization), a member of the site staff will confirm a subject's eligibility with regard to the information they have reported in their electronic diary during screening. If the information captured in the diary deems them eligible, and they continue to meet the inclusion criteria, which includes meeting the Rome III criteria for IBS with constipation, the subject will be randomized into a treatment group.

12-Week Treatment Period	During the 12-week double-blind treatment period, subjects will record daily assessments including: frequency and timing of bowel movements; sensation of complete bowel emptying; consistency of bowel movements (BSFS); degree of straining, worst abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness and abdominal cramping; and use and timing of rescue medication. Subjects will also record weekly assessments including: adequate relief of IBS symptoms, degree of relief of IBS symptoms, IBS severity, and constipation severity. The IBS-QOL questionnaire will be administered during screening, at the end of treatment and at the end of the RW period; and Treatment Satisfaction will be evaluated monthly. The subject will return for study visits every two or four weeks (see schedule of events). Subjects will undergo safety assessments at these visits, which may include a physical exam, ECG, vital signs, and clinical labs. Adverse events and concomitant medications will be recorded. Medication compliance will be monitored and the subjects will be given additional study drug as appropriate.
4-Week RW Period	At the end of the treatment period, subjects who complete the study in the tenapanor group will be randomized to either tenapanor 50 mg BID or placebo BID (1:1) and subjects who complete the study in the placebo group will be assigned to receive tenapanor 50 mg BID. During the 4-week RW period, subjects will continue to record daily and weekly assessments, update concomitant medication as necessary and update adverse events information as appropriate. At the end of the 4-week RW period subjects will return to the clinic for safety assessments, which may include a physical exam, ECG, vital signs, and clinical labs.
General Inclusion/Exclusion Criteria	Inclusion Criteria: • 18 to 75 years old • Females must be of non-childbearing potential; either postmenopausal for at least 12 months as confirmed by follicle-stimulating hormone test (if < 60 years old), or surgically sterile (e.g., tubal ligation, hysterectomy, bilateral oophorectomy with appropriate documentation). If of child-bearing potential, must have negative pregnancy test at Visits 1 and 2, and confirm the use of one of the appropriate means of contraception as listed in Section 5.2. • Males must agree to use an appropriate method of barrier contraception (e.g., latex condom with a spermicidal agent) or have documented surgical sterilization • Subject is ambulatory

	• Subject meets definition of IBS-C using Rome III Criteria for the Diagnosis of IBS • Subject meets screening eligibility criteria (see below) • A colonoscopy based on AGA guidelines; every 10 years at ≥ 50 years old, or the occurrence of any warning signs (i.e., unexplained weight loss, non-hemorrhoid blood in stools) • Ability to communicate well with the Investigator and to comply with the requirements of the entire study, including an understanding of how to use the touch-tone telephone electronic diary. • Written informed consent and a willingness to participate in the study as it is described. • Daily access to a touch tone telephone. Exclusion Criteria: • Functional diarrhea as defined by Rome III criteria • IBS with diarrhea (IBS-D), mixed IBS (IBS-M), or unsubtyped IBS as defined by Rome III criteria • Diagnosis or treatment of any clinically symptomatic biochemical or structural abnormality of the GI tract within 6 months prior to screening, or active disease within 6 months prior to screening; including but not limited to cancer, inflammatory bowel disease, diverticulitis, duodenal ulcer, erosive esophagitis, gastric ulcer, pancreatitis (within 12 months of screening), cholelithiasis, amyloidosis, ileus, non-controlled GERD, gastrointestinal obstruction, ischemic colitis or carcinoid syndrome. • Subject has a potential CNS cause of constipation (e.g., Parkinson's disease, spinal cord injury, or multiple sclerosis) • Use of medications that are known to affect stool consistency (Prohibited Medications), including fiber supplements, anti-diarrheals, cathartics, antacids, opiates, prokinetic drugs, laxatives, enemas, antibiotics during the screening period; unless specified as rescue medication, and used accordingly o Patients on a stable, continuous regimen of fiber, bulk laxatives, stool softeners, or probiotics for the 30 days prior to the screening visit are allowed, provided they agree to maintain a stable regimen throughout the trial • Subject has a history or current evidence of laxative abuse

	(in the clinical judgment of the physician) • Hepatic dysfunction (ALT [SGPT] or AST [SGOT] >2.5 times the upper limit of normal) or renal impairment (serum creatinine > 2mg/dL) • Any evidence of or treatment of malignancy (other than localized basal cell, squamous cell skin cancer or cancer *in situ* that has been resected) within the previous year • Any surgery on the stomach, small intestine or colon, excluding appendectomy or cholecystectomy (unless within 60 days of screening visit) • Pregnant or lactating women • A major psychiatric disorder (DSM-III-R or DSM-IV) including major depression or other psychoses that has required hospitalization in the last 3 years. History of attempted suicide or uncontrolled bipolar disorder • Alcohol or substance abuse in the last year • Participation in other clinical trials within 1 month prior to Day –14 (beginning of screening period) • Clinical evidence of significant cardiovascular, respiratory, renal, hepatic, gastrointestinal, hematologic, neurologic, psychiatric or any disease that may interfere with the subject successfully completing the trial • Subject has been randomized into any Phase 1 or 2 study in which Tenapanor was a treatment • Subject is involved in the conduct and/or administration of this trial as an investigator, subinvestigator, trial coordinator, or other staff member, or the subject is a first degree family member, significant other, or relative residing with one of the above persons involved in the trial • If, in the opinion of the Investigator the subject is unable or unwilling to fulfill the requirements of the protocol or has a condition, which would render the results uninterpretable

Screening Eligibility Criteria to qualify for the Treatment Period	Subject eligibility, according to the IBS symptom information captured in the diary during the 2-week screening period will be determined electronically by the eDiary/IVRS and provided to the clinical site staff upon request. • Subjects must have ≥78 % compliance (≥11 of 14 days) with completing the daily assessments via the touch-tone telephone diary • Subjects must have a weekly stool frequency of <3 CSBMs (complete spontaneous bowel movements) and ≤5 SBMs (spontaneous bowel movements) • For the daily worst abdominal pain assessment, subjects must have an average weekly abdominal pain score of ≥3 on an 11 point numerical rating scale (NRS) • Rescue medication as defined in Section 5.5 (laxative, enema, and/or suppository) usage for ≤2 of the 14 days; none within 48 hours prior to randomization • No use of a prohibited medication, except rescue medication as defined in Section 5.5 • No watery stools (Type 7 on the Bristol Stool Form Scale; for any SBM, or loose (mushy) stools (Type 6 on the BSFS) for >1 SBM
Efficacy Variables:	Primary: • 6/12 week overall responder rate (weekly responder for 6/12 weeks for both CSBM and abdominal pain, described below) vs placebo Key Secondary: • 6/12 week overall CSBM responder rate (weekly responder for 6/12 weeks; ≥ 1 CSBM from baseline) vs placebo • 6/12 week overall abdominal pain responder rate (weekly responder for 6/12 weeks; decrease of ≥30% of worst abdominal pain from baseline) vs placebo • 9/12 week overall responder rate (weekly responder for 9/12 weeks for both CSBM and abdominal pain, described below) vs placebo • 9/12 week overall CSBM responder rate (weekly responder for 9/12 weeks; ≥ 1 CSBM from baseline and ≥ 3 CSBM) vs placebo • 9/12 week overall abdominal pain responder rate (weekly responder for 9/12 weeks; decrease of ≥30% of worst abdominal pain from baseline) vs placebo • Durable overall responder rate (weekly responder for 9/12 weeks and 3 of the last 4 weeks for both CSBM and

	abdominal pain) vs placebo • Durable overall CSBM responder rate (weekly responder for 9/12 weeks and 3 of the last 4 weeks; ≥ 1 CSBM from baseline and ≥ 3 CSBM) vs placebo • Durable overall abdominal pain responder rate (weekly responder for 9/12 weeks and 3 of the last 4 weeks; decrease of ≥30% of worst abdominal pain from baseline) vs placebo <u>Other Secondary Variables</u> • Daily/weekly assessments of other bowel habits including: frequency of CSBMs, frequency of spontaneous bowl movements (SBMs), stool consistency, degree of straining, worst abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness, and abdominal cramping, IBS severity, constipation severity, IBS-QOL, adequate relief of IBS symptoms, degree of relief of IBS symptoms, and treatment satisfaction.
Statistical Considerations	Summary tabulations will be presented that will display descriptive statistics for each treatment group. For subject disposition, demographic and baseline characteristics, medical history, gastrointestinal disease history, and prior medications, an overall column (i.e., all subjects combined) will be included. For continuous variables, descriptive statistics will include the number of subjects, mean, standard deviation, minimum, median, and maximum values. For categorical variables, descriptive statistics will include the number and percent of subjects in each category. All subjects who meet the study entry inclusion/exclusion criteria, receive at least one dose of study drug, and have at least one valid week of efficacy assessment data (minimum of 4 days) will be included in the ITT analysis set. Subjects will be analyzed according to the treatment group into which they were randomized. The ITT analysis set will be the primary analysis set for efficacy analysis. Responder rate efficacy variables will be analyzed using a Cochran-Mantel-Haenszel (CMH) test with pooled investigator site as a stratification (adjustment) variable. Summary statistics will include the pairwise risk difference with placebo along with the asymptotic 95% confidence interval (CI). The adjusted relative risk (adjusted for pooled investigator site) will be based on the ratio of responder rates for placebo versus tenapanor. The 95% CI versus placebo will also be presented for the adjusted relative risk.

	Continuous efficacy variables will be analyzed using an analysis of covariance (ANCOVA) or analysis of variance (ANOVA) model. The ANCOVA model will have terms for pooled investigator site, treatment group, and baseline as the covariate. The ANOVA model will have terms for pooled investigator site and treatment group. The hypotheses will be based on the LS means difference from placebo. Safety analyses will include summaries for adverse events, clinical laboratory tests, vital signs, 12-lead ECGs, and physical exams. Compliance and concomitant medications will also be summarized.

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1. LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransaminase
BM	Bowel movement
BMI	Body mass index
BQL	Below quantitation limit
BSFS	Bristol stool form scale
BUN	Blood urea nitrogen
CIC	Chronic idiopathic constipation
CKD	Chronic kidney disease
CMH	Cochran-mantel-haenszel
CO_2	Carbon dioxide
CRA	Clinical research associate
CRC	Child resistant closure
CRF	Case report form;
CRO	Contract research organization
CSBM	Complete spontaneous bowel movement
CTCAE	Common terminology criteria for adverse events
DSM	Diagnostic and statistical manual of mental disorders
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ESRD	End-stage renal disease
FDA	Food and drug administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
H+	Hydrogen

HDPE	High density polyethylene
HEK	Human embryonic kidney cells
hERG	Human ether-a-go-go related gene
HPMC	Hydroxypropylmethylcellulose
IB	Investigator's brochure
IBS	Irritable bowel syndrome
IBS-C	Constipation predominant irritable bowel syndrome
IBS-D	Diarrhea predominant irritable bowel syndrome
IBS-M	Mixed irritable bowel syndrome (constipation and diarrhea)
IBS-QOL	Irritable bowel syndrome quality of life questionnaire
ICF	Informed consent form
ICH	International conference on harmonization
IEC	Independent ethics committee
IKr	Current amplitude
IRB	Institutional review board
ITT	Intent to treat
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LS	Least squares
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Drug Regulatory Activities
Na+	Water/sodium
NHE_3	Sodium-hydrogen antiporter 3
NOAEL	No observed adverse effect level
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug

OBD	Opioid bowel dysfunction
OC	Observed case
P	Probability; p-value
PD	Pharmacodynamic
PK	Pharmacokinetic
PRO	Patient reported outcome
QA	Quality assurance
QD	Once daily
RBC	Red blood cell
RW	Randomized withdrawal
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBM	Spontaneous bowel movement
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event
TLF	Tables, listings, and figures
WBC	White blood cell count
WHO	World health organization
WHODRL	World health organization drug reference library

2. INTRODUCTION AND STUDY RATIONALE

A major function of the gastrointestinal (GI) tract is to maintain intestinal water/sodium (Na+) homeostasis through a delicate balance of secretory and absorption mechanisms. The Na+/hydrogen (H+) antiporter NHE3 plays a dominant role in the Na+ re-uptake process. Tenapanor (also known as RDX5791 and AZD1722) is a GI-acting NHE3 inhibitor. Tenapanor is a minimally systemic, small molecule under investigation for the treatment of constipation-related diseases such as chronic idiopathic constipation (CIC), constipation predominant irritable bowel syndrome (IBS-C), and opioid bowel dysfunction (OBD). The proposed mechanism of action of tenapanor is to reduce Na+ re-uptake. This decrease in Na+ uptake increases the net fluid volume in the GI tract. Restoration of normal luminal fluid content facilitates intestinal transit and stimulates motility.

This phase 3, multi-center, randomized, double blind, placebo-controlled, multi-center study will evaluate the safety and efficacy of tenapanor in subjects with constipation predominant IBS (IBS-C) as defined by the Rome III criteria and who have active disease as determined during a two-week screening period. Subjects who qualify and are randomized into the study will receive tenapanor 50 mg BID or matching placebo BID for 12 consecutive weeks. At the end of this treatment period, there will be a four-week randomized withdrawal (RW) period. For the RW period, subjects who received tenapanor during the 12-week treatment period will be randomized to receive either tenapanor 50 mg BID or placebo BID and those subjects who received placebo during the 12-week treatment period will receive tenapanor 50 mg BID; this will all be performed under double-blind conditions.

2.1. Scientific Background

2.1.1 Overview of IBS

Irritable bowel syndrome (IBS) is the most common disorder seen by gastroenterologists and is characterized by abdominal pain with associated alterations in bowel function. These changes in bowel patterns may manifest as diarrhea, constipation or an alternation between the two. As there are no pathognomonic, laboratory, endoscopic or radiographic abnormalities found in association with IBS it is considered a functional gastrointestinal (GI) disorder. The chronic nature of the multiple symptoms of IBS, combined with the lack of effective treatments, leads to significant health care resources being used by IBS subjects and impairment of subjects' well-being and functional ability. For research and regulatory purposes, the diagnosis of IBS has been described by the Rome III criteria as summarized in Section 14 (Appendix A).

2.2. Description of Investigational Drug

Tenapanor is chemically described as: (S)-N,N'-(10,17-dioxo-3,6,21,24-tetraoxa-9,11,16,18-tetraazahexacosane-1,26-diyl)bis(3-((S)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl) benzenesulfonamide) dihydrochloride. Its empirical formula is $C_{50}H_{68}Cl_6N_8O_{10}S_2$.

Tenapanor (as the dihydrochloride salt) drug product will be supplied as white to off-white oval biconvex film-coated tablets with the following excipients: [redacted] Tenapanor will be supplied at a dosage strength of 50 mg. Tablets are packaged in an opaque white HDPE (high-density polyethylene) bottle (66/bottle) with a white polypropylene CRC closure and induction seal plus desiccants. Tablets of tenapanor should be stored in the original packaging between 2°C and 30°C. Temperature excursions are allowed from -30°C to 50°C excursions for a maximum of 1 week.

2.3. Previous Human Experience

2.3.1 Safety

Tenapanor has been studied in 14 clinical trials in healthy volunteers, IBS-C, chronic kidney disease (CKD), and end-stage renal disease (ESRD) patients; greater than 1000 subjects have received tenapanor. In the single- and multiple-ascending dose phase 1 clinical trial where tenapanor was administered once a day, there were very few treatment emergent adverse events. In the SAD phase, 3 RDX5791-treated subjects (two 50 mg [33%], one 150 mg [17%]) and 2 placebo-treated subjects (20%) reported AEs. In the MAD phase, 11 tenapanor-treated subjects (two 3 mg [25%], two 10 mg [25%], four 30 mg [50%], and three 100 mg [36%]) and 1 placebo-treated subject (13%) reported AEs. The majority of AEs in both phases were mild in severity and not considered to be related to study drug administration.

In the Phase 1 dosing regimen clinical trial the most common TEAEs were gastrointestinal disorders, including abdominal pain (9.5% and 14.3% of subjects in the total tenapanor and placebo groups, respectively), abnormal gastrointestinal sounds (6% and 0%, respectively), and abdominal discomfort (4.8% and 0%, respectively).

In a 4-week Phase 2a study in IBS-C subjects, where tenapanor was administered at 10, 30, and 100 mg QD, the most common TEAEs among tenapanor-treated subjects were diarrhea, urinary tract infection, and headache (5 [4%] subjects each) and abdominal distention, flatulence, and nausea (3 [2%] subjects). No apparent dose relationship was seen with regard to the incidence of these commonly reported adverse events; there were no drug-related SAEs.

In a 12-week Phase 2b study in IBS-C subjects, where tenapanor was administered at 5, 20, and 50 mg BID, treatment with tenapanor was generally well tolerated. The majority of TEAEs were considered mild to moderate in severity. The most frequently reported TEAEs were diarrhea, headache, nausea, and urinary tract infection. Diarrhea was experienced by 0 (0.0%) subjects in the placebo group, 7 (8.0%) subjects in the tenapanor 5 mg BID group, 11 (12.4%) subjects in the tenapanor 20 mg BID group, and 10 (11.2%) subjects in the tenapanor 50 mg BID group. The most frequently reported drug-related TEAEs were diarrhea, headache,

and abdominal pain. No deaths occurred during the study. Four subjects had an SAE: 1 subject in the placebo group (osteomyelitis), 2 subjects in the tenapanor 5 mg BID group (laryngeal neoplasm and urinary tract infection), and 1 subject in the tenapanor 20 mg BID group (small intestinal obstruction). None of the SAEs were considered to be related to study drug.

The most common adverse events that led to discontinuation of study drug were diarrhea (3 [3.4%] subjects each in the tenapanor 5 mg, 20 mg, and 50 mg BID groups) and abdominal distension (3 [3.4%] subjects in the tenapanor 5 mg BID group). No other specific TEAE (preferred term) led to discontinuation for more than 2 subjects in any treatment group.

There were no clinically meaningful changes from baseline in laboratory tests, vital signs, ECGs, or physical examination findings. No apparent dose relationship was seen with regard to the incidence of these commonly reported adverse events; there were no drug-related SAEs.

2.3.2 Efficacy

2.3.2.1 Phase 2a study of Tenapanor (10, 30, 100 mg QD) in IBS-C subjects

[redacted]

2.3.2.2 Phase 2b study of Tenapanor (5, 20, 50 mg BID) in IBS-C subjects

[redacted]

2.4. Dose Rationale

Results from the Phase 2b study in IBS-C demonstrated that tenapanor 50 mg BID had statistically significant effects in the primary endpoint of CSBM responder rate with consistent effects in both overall and abdominal pain responder rates. Results from this study also demonstrated that 20 mg BID (the next lowest dose) did not have statistically significant effects in key endpoints. Based on results from this double-blind, placebo-controlled study, 50 mg BID was selected as the dose for this pivotal phase 3 clinical trial.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is:

- To assess the efficacy of tenapanor 50 mg for the treatment of IBS-C when administered twice daily (BID) for 12 consecutive weeks.

3.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the safety and tolerability of tenapanor 50 mg when administered twice daily (BID) for 12 consecutive weeks.
- To assess the efficacy of tenapanor 50 mg BID after a 4-week placebo controlled randomized withdrawal period

3.3. Exploratory Objective

The exploratory objective of this study is:

- To collect and store DNA for future exploratory research into plasma biomarkers and genes/genetic variation related to the gastrointestinal disease area or that may influence response (i.e., distribution, safety, tolerability and efficacy) to tenapanor

4. INVESTIGATIONAL PLAN

This is a Phase 3, multi-center, randomized, double-blind, placebo controlled study of tenapanor in subjects with IBS-C. Patients who are 18 to 75 years old, meeting the definition of IBS-C as defined by the Rome III Criteria for the Diagnosis of IBS (see Appendix A) will undergo a battery of screening procedures to determine eligibility for the trial. A 2:1 screen to randomization ratio is expected.

The study will consist of a 2-week screening period, a 12-week treatment period, and a 4-week randomized withdrawal period.

Approximately 2 weeks prior to study randomization, prospective subjects may be

assessed with respect to their meeting the eligibility requirements of the study.

At the beginning of the 2-week screening period (Day -14), subjects will be questioned with respect to their eligibility for the study. Those that meet the basic requirements will be asked to provide written informed consent. The basic screening assessments will include: evaluation of the inclusion/exclusion criteria, medical history (including details about co-morbid disorders), physical exam, vital signs, ECG, and clinical laboratory tests, including urinalysis. Subjects must discontinue the use of all prohibited medications at Visit 1 (Screening/Day -14) for the duration of the study, as referenced in Section 5.6. During the screening period, subjects will self-report daily information about the status of their IBS symptoms via a touch-tone telephone diary. Each day, entries into the telephone diary (IVRS diary) must occur between 6PM and 11:59PM (local time). This will include information about their stool frequency, stool consistency, straining, abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness, abdominal cramping, and rescue medication usage. IBS severity, and constipation severity will be collected weekly through the IVRS diary. Subject compliance with the electronic diary will be monitored actively by the site staff and by the electronic diary system.

At the end of the screening period, prior to the subject returning for Visit 2 (Randomization), a member of the site staff will confirm a subject's eligibility with regard to the information they have reported in their electronic diary during screening. If the information captured in the diary deems them eligible, and they continue to meet the inclusion criteria at Visit 2, a member of the site staff will randomize the subject into a treatment group using an interactive web-response system (IWRS).

Subjects will be randomized into a treatment group according to a computer-generated central randomization schema. All subjects who receive at least one dose of study drug, with at least one valid week of efficacy assessment data will be included in the intention-to-treat (ITT) analysis set. All subjects who receive at least one dose of study drug will be included in all analyses of safety data.

During the 12-week double-blind treatment period and the 4-week double-blind randomized withdrawal period, subjects will continue to record daily and weekly assessments via a touch-tone telephone diary system as instructed. Subjects will be seen weeks 2, 4, 8, and 12 (Days 15, 29, 57, and 85) during the treatment period and week 2 (Day 99) of the RW period for study assessment visits. Subject compliance with daily diary entries will be monitored on an ongoing basis as described above. Subject compliance with study drug will also be monitored closely by clinical site staff throughout the study

Subjects will return to the site at the end of the 4-week randomized withdrawal period (week 16, Day 113) to obtain safety and other end-of-study information.

5. STUDY POPULATION

5.1. General Considerations

Approximately six-hundred (600) subjects who meet all of the inclusion criteria, none of the exclusion criteria and demonstrate active IBS-C during a 2-week screening

period will be randomized into the study at approximately 100 to 120 US clinical centers.

5.2. Inclusion Criteria

Subjects meeting all of the following inclusion criteria will be eligible for enrollment:

1. 18 to 75 years old
2. Females must be of non-childbearing potential; either postmenopausal for at least 12 months as confirmed by follicle-stimulating hormone test (if < 60 years old), or surgically sterile (e.g., tubal ligation, hysterectomy, bilateral oophorectomy with appropriate documentation). If of child-bearing potential, must have negative pregnancy test at Visits 1 and 2, and confirm the use of one of the following appropriate means of contraception:
   - oral birth control pills administered for at least one monthly cycle prior to study drug administration,
   - contraceptive patch worn for at least one monthly cycle prior to study drug administration,
   - progesterone implants,
   - IUDs,
   - abstinence from intercourse for two weeks prior to the study drug administration, throughout the 12-week treatment phase, and the 4-week randomized withdrawal phase, or
   - double barrier method,
   - sterilization of one or both partner(s).
3. Males must agree to use an appropriate method of barrier contraception (e.g., latex condom with a spermicidal agent) or have documented surgical sterilization
4. Subject is ambulatory
5. Subject meets definition of IBS-C using Rome III Criteria (see Appendix A) for the Diagnosis of IBS
6. Colonoscopy requirements
   - Subjects, age 50 years or older, must have had a colonoscopy within 10 years of enrollment (American Gastroenterological Association guidelines).
   - Patients of any age with unexplained warning symptoms (e.g., lower gastrointestinal bleeding, iron-deficiency anemia, clinically significant weight loss, systemic signs of infection or colitis) must have had a colonoscopy, with non-significant findings, after the onset or worsening of the warning symptoms.

7. Ability to communicate well with the Investigator and to comply with the requirements of the entire study, including an understanding of how to use the touch-tone telephone electronic diary
8. Written informed consent and a willingness to participate in the study as it is described
9. Daily access to a touch tone telephone

5.3. Exclusion Criteria

Subjects meeting one or more of the following exclusion criteria are not to be enrolled in the study:

1. Functional diarrhea as defined by Rome III criteria (see Appendix A)
2. IBS with diarrhea (IBS-D), mixed IBS (IBS-M), or unsubtyped IBS as defined by Rome III criteria (see Appendix A)
3. Diagnosis or treatment of any clinically symptomatic biochemical or structural abnormality of the GI tract within 6 months prior to screening, or active disease within 6 months prior to screening. Including but not limited to cancer, inflammatory bowel disease, diverticulitis, duodenal ulcer, erosive esophagitis, gastric ulcer, pancreatitis (within 12 months of screening), cholelithiasis, amyloidosis, ileus, non-controlled GERD, gastrointestinal obstruction or carcinoid syndrome
4. Use of medications that are known to affect stool consistency as described in Section 5.6 (Prohibited Medications). Note: Patients on a stable, continuous regimen of fiber, bulk laxatives, stool softeners, or probiotics during the 30 days before the screening visit are allowed to continue, provided they maintain a stable dosage throughout the trial.
5. Clinical evidence of significant cardiovascular, respiratory, renal, hepatic, gastrointestinal, hematologic, neurologic, psychiatric or any disease that may interfere with the subject successfully completing the trial
6. The subject has a history or current evidence of laxative abuse (in the clinical judgment of the physician)
7. Hepatic dysfunction (ALT [SGPT] or AST [SGOT] >2.5 times the upper limit of normal) or renal impairment (serum creatinine > 2mg/dL)
8. Any evidence of or treatment of malignancy (other than localized basal cell, squamous cell skin cancer or cancer *in situ* that has been resected) within the previous year
9. Any surgery on the stomach, small intestine or colon, excluding appendectomy and cholecystectomy
10. If, in the opinion of the Investigator the subject is unable or unwilling to fulfill the requirements of the protocol or has a condition, which would render the results uninterpretable

11. A major psychiatric disorder (DSM-III-R or DSM-IV) including major depression or other psychoses that has required hospitalization in the last 3 years. History of attempted suicide or uncontrolled bipolar disorder.
12. Alcohol or substance abuse in the last year
13. Subject has been randomized into any Phase 1 or 2 study in which tenapanor was a treatment
14. Subject is involved in the conduct and/or administration of this trial as an investigator, sub-investigator, trial coordinator, or other staff member, or the subject was a first degree family member, significant other, or relative residing with one of the above persons involved in the trial
15. Participation in other clinical trials within 1 month prior to Day –14 (beginning of screening period)

5.4. Entry Criteria at End of 2-Week Screening Period

In order to be eligible for randomization, subjects must satisfy inclusion/exclusion criteria as described in Sections 5.2 and 5.3 and meet the subject reported outcome criteria collected during the 2-week screening period as described below.

Subject eligibility, according to the IBS symptom information captured in the diary during the 2-week screening period, will be determined electronically by the interactive voice-response system and provided to the clinical site staff upon request.

- Subjects must have ≥78 % compliance (≥11 of 14 days) with completing the daily assessments via the touch-tone telephone diary
- Subjects must have a weekly stool frequency of <3 CSBMs (complete spontaneous bowel movements) and ≤5 SBMs (spontaneous bowel movements)
- Subjects must have a mean stool consistency score of ≤3 using the 7-point Bristol Stool Form Scale (BSFS) (see Appendix B)
- For the daily assessment of abdominal pain, subjects must have an average weekly abdominal pain score of ≥3 on a 0-10 point scale.
- Rescue medication usage for ≤ 2 of the 14 days; none within 48 hours prior to randomization
- No use of a prohibited medication, except rescue medication as defined in Section 5.5
- No watery stools (Type 7 on the Bristol Stool Form Scale; (see Appendix B) for any SBM, or loose (mushy) stools (Type 6 on the BSFS) for >1 SBM

5.5. Rescue Medication

The following rescue medications are allowed for severe constipation (ie, at least 72 hours after the subject's previous BM or when symptoms become intolerable):

- Bisacodyl 5 mg tablet or 10 mg suppository

Rescue medication is allowed during the screening period, provided that there are no more than 2 uses and that none is used during the 2 days before randomization. Subjects are instructed to contact the investigator prior to taking a rescue medication

for severe constipation, and all rescue medication usage and time of usage must be recorded during the subject's daily call to the IVRS. A bowel movement will not be considered a spontaneous bowel movement (SBM) if it is reported less than 24 hours from the use of a rescue medication.

5.6. Prohibited Concurrent Medications

Administration of any concomitant therapy during the 7 days prior to the screening period, during the screening, treatment or RW periods should be recorded on the appropriate CRF page. The following medications are specifically prohibited from use during the study (including screening and RW periods), unless specified as a rescue medication and used according to the procedure outlined in Section 5.5.

- Antidiarrheals
- Antacids which contain aluminum and/or magnesium (if used more than 3 days per week)
- Enemas (except as defined in Section 5.5)
- Antinausea agents (e.g., benzquinamide, trimethobenzamide)
- Antispasmodic agents (e.g., Donnatal®, Librax®)
- Laxatives or stool softeners (except a stable dose as defined in Section 5.3, #4)
- Prokinetic agents (e.g., cisapride, metoclopramide)
- Macrolide antibiotics (e.g., erythromycin, azithromycin)
- Cholestyramine or WelChol®
- 5-HT_3 antagonists (e.g., alosetron, ondanestron)
- 5-HT_4 agonists (e.g., tegaserod)
- Bismuth preparations
- Anticholinergics (e.g., dicyclomine)
- Narcotics and narcotic containing analgesics, including tramadol
- Iron supplements (with the exception of multivitamins containing Iron and those individuals on a stable dose for > 30-days prior to screening period of Iron supplements)
- NSAIDS (if used more than 3 days per week); Aspirin ≤ 325 mg per day is allowed
- All other analgesics (if used more than 3 days per week)
- Anti-Parkinson agents (e.g. levodopa, deprenyl)
- Antipsychotics, allowed if on a stable dose for > 30-days prior to screening period
- Anticonvulsants used for seizure disorders
- Antidepressants, allowed, if on a stable dose for > 30-day prior to screening period
- Stimulants and amphetamine-like drugs
- Misoprostol, alone or in combination
- Lubiprostone (Amitiza®) or Linaclotide (Linzess®)

5.7. Removal of Subjects from Therapy or Assessment

Subjects will be discontinued from the study if any of the following conditions apply:

1. A subject experiences a study drug related serious adverse event.
2. A subject experiences severe diarrhea defined by a Bristol Stool Form Score

(Appendix B) of ≥ 6 and stool frequency ≥ 7/day (Common Terminology Criteria for Adverse Events [CTCAE] v4.0, Grade 3) for 2 consecutive days.

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator may remove a subject if he/she feels this action is in the best interest of the subject.

When a subject withdraws from the study, all of the necessary safety and tolerability assessments as described for Visit 8 should be obtained. Subjects experiencing adverse reactions should be followed until the reaction has resolved or is clearly determined to be due to a subject's stable or chronic condition. Appropriate supportive and/or definitive therapy will be administered as required.

Subjects will not be replaced.

The reason(s) for a subject's withdrawal from the study and their final assessments are to be recorded on the appropriate electronic case report form (eCRF) page.

6. TREATMENTS

6.1. Identity of Investigational Product

Tenapanor (as the dihydrochloride salt) drug product will be supplied as white to off-white oval biconvex film-coated tablets.. Matched placebo tablets will also be provided.

6.2. Packaging, Storage, and Labeling

The study drug will be supplied in white square HDPE bottles with child resistant polypropylene CRC closures with an induction seal plus desiccants. Each bottle will contain sixty-six (66) tablets.

Tenapanor and placebo tablets should be stored in the original packaging between 2°C and 30°C. Temperature excursions are allowed from -30°C to 50°C excursions for a maximum of 1 week.

Each bottle will be labeled with a single panel, double blind label.

6.3. Treatments to be Administered

Study drug will be dispensed only to eligible subjects under the supervision of the Investigator or identified sub-Investigator(s). Eligible subjects will be randomized 1:1 into one of two treatment groups: tenapanor 50 mg BID or placebo BID. Subjects will take one tenapanor tablet or one matching placebo tablet twice daily, immediately prior to breakfast or the first meal of the day and immediately prior to dinner.

Subjects will receive a 4-week supply of drug at Visit 2 (Day 1), Visit 4 (Day 29 ± 3), Visit 5 (Day 57 ± 3 days) and Visit 6 (Day 85 ± 3 days). At Visits 4, 5, 6, and 8 (Day 113 ± 3 days) the subject will be asked to return their unused drug and bottles. All unused study drug and bottles should be returned to the study site. Study drug compliance will be monitored closely by the clinical site staff and will be verified by the study monitor during on-site monitoring visits.

6.4. Randomization and Blinding

Both randomization and blinding techniques will be used in this study to minimize bias. Randomization will occur twice; at Visit 2 for the 12-week treatment phase and at Visit 6 for the 4-week randomized withdrawal period. A computer generated randomization schema will be centrally available via an interactive web response system (IWRS) to all clinical centers that meet the requirements for participation in the study. The IWR system can be accessed by a computer by individuals that have been issued a user ID and password.

In order to double-blind the study, the study drug is labeled in a manner to ensure that neither investigators nor subjects can distinguish between treatment groups.

In the case of a medical emergency where, in the Investigator's judgment, the subject's safety may be compromised without immediate knowledge of the exact treatment received, the Investigator can contact the IWRS help desk.

All reasonable effort should be made to reach the Medical Monitor prior to unblinding. If the treatment is unblinded, the Investigator should immediately contact:

7. SCHEDULE OF ASSESSMENTS

The study flow chart, including all procedures to be performed during the study is presented below. Prior to engaging in any study procedure, each subject must sign and date an informed consent form.

Evaluation	**Screen**	**Treatment Period**					**RW Period**	
Site Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET[h]**
Study Day(s)	**-14**	**1±3**	**15±3**	**29±3**	**57±3**	**85±3**	**99±3**	**113±3**
Informed Consent[a]	X							
Inclusion/Exclusion	X	X						
Demographics	X							
Medical History (including GI history)	X	X[b]						
Prior/Concurrent Medications	X	X	X	X	X	X	X	X
Physical Exam	X					X		X
Vital Signs[c]	X	X	X	X	X	X	X	X
Height	X							
Safety Laboratories	X			X		X		X
Pharmacogenomics blood sample[g]				X[g]		X[g]		X[g]
Biomarker sample	X					X		X
FSH test[d]	X							
Serology	X							
Urine Pregnancy test[d]	X	X		X		X		X
Urinalysis	X			X		X		X
12-lead electronic ECG	X					X		X
IVRS Training/Compliance Check & Reminder	X	X	X	X	X	X	X	

Evaluation	Screen	Treatment Period					RW Period	
Site Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET[h]**
Study Day(s)	**-14**	**1±3**	**15±3**	**29±3**	**57±3**	**85±3**	**99±3**	**113±3**
IBS-QOL PRO		X				X		X
Treatment Satisfaction PRO				X	X	X		X
Randomization		X						
Randomization #2[f]						X		
Daily PROs[e]	X	X	X	X	X	X	X	X
Drug Dispensed/returned		D		D/R	D/R	D/R		R
Adverse Event Assessments			X	X	X	X	X	X

[a]The Informed Consent Form (ICF) must be signed before any study procedures are performed; The ICF may be signed before the Screening Visit.
[b]Medical history for Visit 2; record only changes to Medical history from Visit 1.
[c]Vital signs include systolic and diastolic blood pressure (seated), heart rate, respiratory rate, temperature and body weight.
[d]FSH is performed in post-menopausal women (at screening only); pregnancy tests are performed on all females <60 years of age unless there is a documented method of sterilization, or FSH test confirms post-menopausal status. A positive urine pregnancy test will be verified with a serum pregnancy test.
[e]Daily Patient Reported Outcomes will be collected via a phone diary and will include the following: frequency and time of each Bowel Movement (BM), sensation of complete bowel emptying, stool consistency (BSFS) of each BM, straining, abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness, abdominal cramping, use of and time of rescue medication, IBS severity (weekly), constipation severity (weekly), adequate relief of IBS symptoms (weekly, after randomization), degree of relief of IBS symptoms (weekly, after randomization).
[f]All subjects receiving Placebo will be switched to tenapanor 50 mg BID; Subjects receiving tenapanor 50 mg BID will be randomized 1:1 to receive either tenapanor 50 mg BID or Placebo 50 mg BID.
[g]The pharmacogenomics sample is optional and requires subject to specify acceptability on the informed consent. If a subject opts in, the blood sample can be taken at any one visit after randomization with a scheduled blood draw (Visit 4, 6, or 8).
[h]Procedures described for Visit 8/ET (Early Termination) should be performed on all subjects who withdraw early from the study, if possible.

8. STUDY EVALUATIONS

The assessments to be performed during the study are outlined by study period, visit and study day below. The day of randomization begins the clock for all subsequent visit days and dates.

8.1. Pre-Screening and Screening Period Procedures

Pre-screening may be performed using a telephone questionnaire/script to ascertain preliminary subject eligibility. Potential subjects will be questioned with regard to their relevant medical history, GI history, current symptoms, and ability and interest in participating in a clinical trial.

Each subject must sign and date an informed consent form prior to engaging in any study specific procedures.

8.1.1 Evaluations and procedures at Visit 1 (Day –14)

The procedures outlined for Visit 1 must be completed prior to enrolling the subject into the study. The following procedures will be conducted at Visit 1:

- Informed Consent (must be signed prior to discontinuing any prohibited medications or prior to the conduct of any study-related procedure)
- Inclusion/Exclusion Criteria
- Demographics
- Medical History, including IBS-C history
- Prior and Concomitant Medications
- Physical Exam
- Vital Signs
- Height
- Safety Laboratories
- Biomarker sample
- FSH Test, as appropriate
- Serology
- Urine Pregnancy Test
- Urinalysis
- ECG
- Subjects will be instructed on the use of the telephone diary and begin

calling into the diary the evening of Visit 1 (Day -14)

- Subjects will be instructed to discontinue the use of all prohibited medications as outlined in Section 5.6.

8.1.2 Daily Patient Reported Outcomes (PRO) (Day –14 through Day 113)

Subjects must assess their IBS symptoms daily via the touch-tone telephone diary system between 6PM and 11:59PM (local time):

- Frequency and time of each Bowel Movement (BM)

  The following characteristics of each BM

  - Sensation of complete bowel emptying
  - Stool consistency (BSFS) of each BM
  - Severity of straining for each BM
- Abdominal pain
- Abdominal discomfort
- Abdominal bloating
- Abdominal fullness
- Abdominal cramping
- Use of and time of rescue medication
- IBS severity (weekly)
- Constipation severity (weekly)
- Adequate Relief of IBS Symptoms (weekly, after randomization)
- Degree of Relief of IBS Symptoms (weekly, after randomization)

8.2. Treatment Period Procedures

Each subject must meet the eligibility requirements as outlined in Sections 5.2, 5.3 and 5.4 of this protocol prior to being randomized into the treatment phase of the study.

8.2.1 Evaluations and procedures at Visit 2 (Day 1 ± 3)

Prior to the subjects' return to the clinic for Visit 2, a member of the site staff will confirm the subjects' eligibility in the IWR system. At Visit 2, prior to randomization, the following tests/procedures will be performed and questionnaires completed. After randomization, study drug will be dispensed.

- Inclusion/Exclusion Criteria (confirm eligibility)
- Medical History (changes since last visit)
- Concomitant Medications (changes since last visit)
- Vital signs
- Urine pregnancy test
- IBS-QOL PRO
- Randomization
- Drug Dispensed

8.2.2 Evaluations and procedures at Visit 3 (Day 15 ± 3)

- Vital Signs
- Adverse Events
- Concomitant Medications (changes since last visit)

8.2.3 Evaluations and procedures at Visit 4 (Day 29 ± 3)

- Vital Signs
- Safety Laboratories
- Pharmacogenomics blood sample (if consented)
- Urine Pregnancy Test
- Urinalysis
- Adverse Events
- Concomitant Medications (changes since last visit)
- Treatment Satisfaction PRO
- Drug Returned
- Drug Dispensed

8.2.4 Evaluations and procedures at Visit 5 (Day 57 ± 5)

- Vital Signs
- Adverse Events
- Concomitant Medications (changes since last visit)

- Treatment Satisfaction PRO
- Drug Returned
- Drug Dispensed

8.2.5 Evaluations and procedures at Visit 6 (Day 85 ± 5)

See Sections 8.3 and 8.3.1 for Randomized Withdrawal procedures to occur at the end of the procedures described below for Visit 6.

- Vital Signs
- Physical Exam
- Safety Laboratories
- Pharmacogenomics blood sample (if consented and not performed yet)
- Biomarker sample
- Urine Pregnancy Test
- Urinalysis
- ECG
- Adverse Events
- Concomitant Medications (changes since last visit)
- IBS-QOL PRO
- Treatment Satisfaction PRO
- Drug Returned

8.3. Randomized withdrawal (RW) period procedures

Each subject completing the 12-week treatment period will enter into a 4-week randomized withdrawal (RW) period. Subjects who were receiving placebo will be given tenapanor 50 mg BID. Subjects who were receiving tenapanor 50 mg BID will be randomized via IWRS in a double blind manner to receive either tenapanor 50 mg BID or placebo BID for four weeks. Subjects are expected to continue to record daily and weekly diary information during this time

8.3.1 Evaluations and procedures at Visit 6 (Day 85 ± 5) – RW Period

- Randomization #2 via IWRS
- Drug Dispensed

8.3.2 Evaluations and procedures at Visit 7 (Day 99 ± 5) – RW Period

- Vital Signs
- Adverse Events
- Concomitant Medications (changes since last visit)

8.3.3 Evaluations and procedures at Visit 8 (Day 113 ± 5) – RW Period

- Vital Signs
- Physical Exam
- Safety Laboratories
- Pharmacogenomics blood sample (if consented and not performed yet)
- Biomarker sample
- Urine Pregnancy Test
- Urinalysis
- ECG
- Adverse Events
- Concomitant Medications (changes since last visit)
- IBS-QOL PRO
- Treatment Satisfaction PRO
- Drug Returned

8.4. Safety and Efficacy Assessments

8.4.1 Safety Assessments

Safety assessments will be based on adverse events, clinical laboratory tests, vital signs, ECG, and physical examinations,.

Incidence of adverse events and clinically significant abnormal laboratory values will be determined at the completion of the study. This study will help characterize the safety and tolerability profile of tenapanor 50 mg BID in IBS-C subjects.

Safety assessments are described below.

8.4.1.1 Adverse events

Monitoring of treatment emergent adverse events will be conducted throughout the study beginning on Day 1 (Randomization). Adverse events, including serious adverse events will be recorded in the eCRFs through the end of the 4-week

randomized withdrawal (RW) period. All adverse events should be followed by the investigator until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or concurrent illness(es). Definitions, documentation, and reporting of adverse events are described in detail in Section 9.

8.4.1.2 Medical history and physical examination

An abbreviated medical history will be obtained over the telephone at the time of the prescreening questionnaire (if performed) for the purpose of determining eligibility. A full medical history will be taken at Screening during Visit 1. A complete physical examination will be conducted during Visits 1, 6 and 8.

8.4.1.3 Electrocardiogram

A 12-lead electrocardiogram will be obtained during Visits 1, 6 and 8.

8.4.1.4 Vital signs

Vital signs, including heart rate, respiratory rate, sitting systolic and diastolic blood pressure (SSBP, SDBP), temperature, and body weight will be obtained at all Visits.

8.4.1.5 Clinical laboratory tests

A central laboratory will perform clinical laboratory tests. Blood samples will be drawn from subjects for serum chemistries and hematology at Visits 1, 4, 6 and 8. Urine will be taken for urinalysis at Visits 1, 2 (pregnancy test only), 4, 6, and 8. A FSH test will be performed, as appropriate at Visit 1. See Appendix C for specific laboratory tests.

Clinical laboratory test values that are considered abnormal will be noted as clinically significant or non-clinically significant by the site investigator. Clinical laboratory test values that are out of the normal limits are considered to be abnormal.

Handling and shipment of clinical laboratory samples will be outlined in the Lab Manual.

8.4.2 Efficacy Assessments

Subjects will report efficacy assessments via an interactive voice response system (IVRS) utilizing a touch-tone telephone. Efficacy assessments will be collected daily and weekly, unless otherwise specified, from the beginning of the screening period through the end of the randomized withdrawal period. The daily questions will include information about bowel movement frequency, completeness of bowel emptying, stool consistency, straining, abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness, abdominal cramping, and use of rescue medications. IBS severity and constipation severity will be collected weekly during the screening, treatment, and randomized withdrawal periods. Adequate relief of IBS symptoms and degree of relief of IBS symptoms will be collected weekly during the treatment and randomized withdrawal periods. Treatment satisfaction (Visits 4, 5, 6, and 8) and IBS-QOL (Visits 2, 6, and 8) will also be evaluated during the subjects' site visit.

A script detailing the IVRS diary questions and scales will be supplied to the clinical

site and to the subjects in the form of written subject information material. The following questions will be asked to all subjects on a daily or weekly basis during the screening, treatment and randomized withdrawal periods.

8.4.2.1 Abdominal Pain

"How would you rate your worst abdominal pain over the past 24 hours? Please use the scale where 0 represents no abdominal pain and 10 represents very severe abdominal pain. Please enter a value between 0 and 10 followed by pound or hash sign."

8.4.2.2 Abdominal Discomfort

"How would you rate your abdominal discomfort over the past 24 hours? Please use the scale where 0 represents no abdominal discomfort and 10 represents very severe abdominal discomfort. Please enter value between 0 and 10 followed by pound or hash sign."

8.4.2.3 Abdominal Bloating

"How would you rate your abdominal bloating over the past 24 hours? Please use the scale where 0 represents no abdominal bloating and 10 represents very severe abdominal bloating. Please enter a value between 0 and 10 followed by pound or hash sign."

8.4.2.4 Abdominal Cramping

"How would you rate your abdominal cramping over the past 24 hours? Please use the scale where 0 represents no abdominal cramping and 10 represents very severe abdominal cramping. Please enter a value between 0 and 10 followed by pound or hash sign."

8.4.2.5 Abdominal Fullness

"How would you rate your abdominal fullness over the past 24 hours? Please use the scale where 0 represents no abdominal fullness and 10 represents very severe abdominal fullness. Please enter a value between 0 and 10 followed by pound or hash sign."

8.4.2.6 Bowel Movement Frequency

"How many bowel movements have you had in the past 24 hours?"

8.4.2.6.1 Timing

"Please enter the time of bowel movement <number> using the 12 hour AM/PM format."

"For AM press 1, for PM press 2."

8.4.2.6.2 Sensation of Complete Bowel Emptying (For each bowel movement)

"Did you feel like you completely emptied your bowels? For yes press 1 for no press 2."

8.4.2.6.3 Stool Consistency using BSFS (Appendix B) (For each bowel movement)

"Refer to the Bristol Stool Form Scale given to you. Please enter the number that best describes the consistency of bowel movement <number> following the scale:

Press 1 for separate hard lumps, like nuts (hard to pass)

Press 2 for sausage shaped but lumpy

Press 3 for like a sausage but with cracks on its surface

Press 4 for like a sausage or a snake, smooth and soft

Press 5 for soft blobs with clear cut edges (passed easily)

Press 6 for fluffy pieces with ragged edges, a mushy stool

Press 7 for watery, no solid pieces (entirely liquid)"

8.4.2.6.4 Straining (For each bowel movement)

"How much did you strain during the bowel movement? Please use the following scale. Press 1 for not at all. Press 2 for a little bit. Press 3 for a moderate amount. Press 4 for a great deal. Press 5 for an extreme amount."

8.4.2.7 Rescue medication

If diary was completed the previous day "Have you taken any rescue medication over the past 24 hours? For yes press 1, for no press 2."

If diary was NOT completed the previous day "Have you taken any rescue medication over the past 48 hours? For yes press 1, for no press 2."

If yes. "Please enter the date you took the rescue medication, using the 8 digit format; 2 digits for the month, 2 digits for the day and 4 digits for the year."

"Please enter the time you took rescue medication, using a 12 hour AM/PM format."

"For AM press 1, for PM press 2"

The following questions will be asked once at the end of each week; when these questions are asked they will be the first questions asked to the subjects

8.4.2.8 IBS Severity (weekly)

"How would you rate the severity of your IBS over the past week? Please use the following scale. Press 1 for None. Press 2 for Mild. Press 3 for Moderate. Press 4 for Severe. Press 5 for Very Severe."

8.4.2.9 Constipation Severity (weekly)

"How would you rate the severity of your constipation over the past week? Please use the following scale. Press 1 for None. Press 2 for Mild. Press 3 for Moderate. Press 4 for Severe. Press 5 for Very Severe."

8.4.2.10 Adequate Relief of IBS Symptoms (weekly)

"Have you had adequate relief of your IBS symptoms over the past week? Press 1 for Yes. Press 2 for No."

8.4.2.11 Degree of Relief of IBS Symptoms (weekly)

"How would you rate the degree of relief of your IBS symptoms over the past week? Please use the following scale. Press 1 for Completely relieved. Press 2 for Considerably relieved. Press 3 for Somewhat relieved. Press 4 for Unchanged. Press 5 for Somewhat worse. Press 6 for Considerably worse. Press 7 for As bad as I can imagine."

8.4.2.12 Treatment Satisfaction (completed at site, not IVRS)

At visits 4, 5, 6, and 8, subjects will be questioned about their overall satisfaction with the study drug's ability to relieve IBS; with the following possible answers: 1= not at all satisfied, 2= a little satisfied, 3= moderately satisfied, 4 =quite satisfied, 5= very satisfied

8.4.2.13 Irritable Bowel Syndrome - Quality of Life (IBS-QOL) (completed at site, not IVRS)

On Day 1 (Visit 2), after randomization, and at Visits 6 and 8 (Day 85, at the end of the treatment period; and Day 113, at the end of the randomized withdrawal period), subjects will be questioned about their quality of life. The IBS-QOL (see Appendix D) measures 10 domains found to be relevant to patients with irritable bowel syndrome: emotional health, mental health, health belief, sleep, energy, physical functioning, diet, social role, physical role, and sexual relations. The IBS-QOL consists of 34 questions.

8.5. Total Blood Volume Required for Study

Table 8-1 Approximate Blood Volume per Subject

Test	Number of Samples	Volume (mL)	Total (mL)
Serology (serum)	1	5	5
Hematology (blood)	4	3	12
Chemistry (serum)	4	7	28
Biomarker (seum)	3	7	21
Pharmacogenomics sample (blood)	1	7	7
Total	**13**	**--**	**73**

8.6. Data Quality Assurance

This clinical trial will be monitored according to current Ardelyx Standard Operating Procedures (SOP) or its CRO designee's SOP. Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and

appropriate study sites, review of protocol procedures and the administration of informed consent with the Investigator and associated site personnel prior to study start, and periodic monitoring visits by Ardelyx personnel or its CRO designee. During the trial, the Investigator shall permit Ardelyx or its CRO designee to verify the progress of the trial on site as frequently as necessary. Qualified personnel will review case report form data for accuracy and completeness against source documents during on-site monitoring. Data discrepancies will be resolved with the Investigator or designees, as appropriate. The Investigator shall make the eCRFs and source documents available, provide missing or corrected data and sign the eCRFs. After Ardelyx personnel, or its CRO designee, receive the CRFs, data management personnel will review the forms for completeness, logical consistency and safety. The eCRF must be amended after any inconsistencies found at this review have been resolved. No personal information will be recorded on the eCRFs in accordance with HIPAA regulations.

An independent Quality Assurance (QA) department, Ardelyx designees and/or regulatory authorities may review this trial. This implies that auditors/inspectors will have the right to inspect the trial center(s) at any time during and/or after completion of the trial and will have access to source documents, including the subject's file. By participating in this trial, Investigators agree to this requirement. Measures will be undertaken to protect subject data handed over by the Investigator to Ardelyx and to inspectors against disclosure to unauthorized third parties and subject confidentiality will be maintained at all times.

9. ADVERSE EVENTS

9.1. Adverse Event

An **adverse event** (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product, whether or not the occurrence has causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of the investigational product.

Worsening of IBS symptoms is not considered an adverse event unless the frequency and/or severity of the symptom(s) is outside of what the subject considers normal for their IBS.

9.2. Severity

The term “severe” is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction). Even though the event itself may be of relatively minor medical significance (such as a severe headache), this is not the same as “serious,” which is based on subject/event outcome or action criteria as described above and are usually associated with events that pose a threat to a

subject's life or functioning. A severe adverse event is not necessarily serious. For example, persistent nausea of several hours duration may be considered severe nausea but not meet the definition of a SAE. On the other hand, a stroke resulting in only a minor degree of persistent disability may be considered mild, but would be defined as a SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

For both serious and non-serious adverse events, the Investigator must determine the severity of the event using the following definitions:

Mild The event does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance but does not cause any limitation in usual activity.

Moderate The event produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment and may cause some limitation in usual activity.

Severe The event produces significant impairment or incapacitation and is a definite hazard to the subject's health.

9.3. Unexpected Adverse Drug Experience

An unexpected adverse experience is any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator's Brochure, or if an Investigator's Brochure is not required or available, which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition refers to an adverse drug experience that has not previously been observed (e.g., included in the Investigator's Brochure) rather than from the perspective of such an experience not being anticipated from the pharmacological properties of the pharmaceutical product.

9.4. Causality

Association of adverse events to the study drug will be made using the following definitions:

Not related: The event is most likely produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs, and does not follow a known response pattern to the study drug, or the temporal relationship of the event to study drug administration makes a causal relationship unlikely

Possibly-related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs

Probably-related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs.

9.5. Serious Adverse Event

A **serious adverse event** (SAE) is any untoward medical occurrence, that at any dose, regardless of causality:

- results in death.
- is life-threatening. Life threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form might have caused death.
- requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- is a congenital anomaly/birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

9.6. Procedures for Recording and Reporting AEs and SAEs

Adverse events, both serious and non-serious, will be reported between Day 1 (Randomization) and the final visit (up to Day 113, Visit 8). Medical events that occur between the signing of the informed consent and the first dose of study drug will be documented as part of the subject's medical history and recorded on the appropriate eCRF page.

All adverse events spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory tests or other clinical finding is considered an adverse event and must be recorded on the appropriate pages of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event or diagnosis.

All serious adverse events occurring during the course of the study must be reported by email, or fax immediately to:

[redacted]

In no event shall a SAE be reported more than twenty-four (24) hours after the Investigator becomes aware of such event. The report of an SAE by the Investigator must provide the following minimal information: protocol number, subject number, subject's initials and date of birth, nature of the adverse event and attributes such as the severity of the event and causality. Events will be considered suspected adverse drug reactions if classified by the Investigator as possibly-related or probably-related.

A report of a SAE by telephone must always be confirmed by a written, more detailed report within 24 hrs of the Investigator becoming aware of the event. The SAE Reporting Forms are provided to each clinical study site in the Study Manual. The Investigator should provide the following documentation at the time of notification, if available:

SAE Reporting Form
Concomitant and support medication pages;
Relevant diagnostic reports;
Relevant laboratory reports;
Admission notes; if applicable
Hospital discharge summary; if applicable

[redacted]

It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of all SAEs, as well as any unanticipated problems that involve significant risk to subjects. A copy of the IRB/IEC notification should be placed in the sites' regulatory binder.

9.7. Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, will be recorded on the eCRFs up to and including the final visit (Day 113, Visit 8). All adverse events should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or concurrent illness(es).

Follow-up data concerning the SAE (e.g., diagnostic test reports, physician's summaries, etc.) must also be submitted to the Sponsor as they become available, preferably by facsimile. All serious adverse events, as well as any unanticipated problems that involve significant risk to subjects, must be promptly reported by the Investigator to his/her Institutional Review Board (IRB). Should the FDA or other

pertinent regulatory authorities require that Ardelyx submit additional data on the event, the Investigator will be asked to provide those data to Ardelyx in a timely fashion.

The Investigator will review each serious adverse event report and further evaluate the relationship of the adverse event to the study drug and to the subject's underlying disease. Based on the Investigator assessment of the adverse event, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of other subjects participating in the clinical study. If the discovery of a serious and unexpected adverse event related to the study drug raises concern over the safety of its continued administration to subjects, the Sponsor will take immediate steps to notify the FDA and other pertinent regulatory authorities and all Investigators participating in clinical studies of the study drug.

Any serious adverse event that occurs at any time after completion of the study, which the Investigator considers to be related to study drug, must be reported to Ardelyx within forty-eight (48) hours of the Investigator becoming aware of the event.

9.8. Pregnancy

Pregnancy by definition is not considered to be a serious adverse event unless the pregnancy or the outcome meets the criteria in Section 9.5.. However, pregnancy in subjects that have received the study drug must be followed to assess congenital anomalies.

10. STATISTICAL CONSIDERATIONS

This is a Phase 3, multi-center, randomized, double-blind, placebo controlled study of tenapanor in subjects with IBS-C. Treatment to be administered consists of two treatment groups: placebo and tenapanor 50 mg twice daily (BID, total daily dose of 100 mg) for 12 consecutive weeks. At the end of the treatment period there will be a 4-week randomized withdrawal (RW) period in which all subjects in the placebo arm will be given tenapanor 50 mg BID and subjects in the tenapanor arm will be randomized 1:1 to receive either placebo or tenapanor 50 mg BID; this will be performed in a double-blind manner. At least 600 subjects will be enrolled at approximately 100-120 US clinical centers. Each center is expected to enroll approximately six (6) subjects, however, enrollment is competitive and centers will be allowed to enroll subjects beyond the expected site projection.

A formal statistical analysis plan (SAP) will be developed, finalized, and signed-off on prior to the database lock and unblinding of treatment assignment. It is anticipated that the SAP will be submitted prior to the first subject being enrolled in the study. This plan will confirm the analysis sets used in the analysis, outline all data handling conventions, and specify all statistical methods to be used for all safety and efficacy analyses. The SAP will pre-specify exploratory and sensitivity analyses as additions to analyses included in the protocol. In particular, the primary analysis and key secondary analyses will remain the same. If after the data has been unblinded and additional analyses are implemented or planned analyses are changed, such deviations

will be documented in the clinical study report. Any implications for the interpretation of the trial results will be addressed. A set of table, listing, and figure shells will also be part of this plan for internal use . Any changes to the statistical considerations described in Section 10 of this protocol will be addressed in the SAP and will not be part of a protocol amendment.

10.1. Determination of Sample Size

A sample size of 300 in each treatment group would achieve 95% power to detect a difference of 0.15 (15%) between the placebo and tenapanor 50 mg BID 6/12 week overall responder rate when the tenapanor 50 mg BID responder rate is at least 45% under the alternative hypothesis and the responder rate in the placebo group is no closer than 15% from tenapanor 50 mg BID. The test statistic used was the two-sided Fisher's exact test with significance level of 0.050 (5%). This sample size also has 80% power to detect an 11.6% difference in responder rates between the treatment groups when the responder rates are in the same range as above.

10.2. Randomization and Stratification

A computer generated randomization schema will be made available centrally to all clinical centers that meet the requirements for participation in the study via an interactive web response system (IWRS). The IWRS can be accessed with a computer by individuals with a study-issued user ID and password implemented to limit access and document a user log. The packaging and labeling of the study drug kits will be based on a separate drug packaging randomization schedule. Upon satisfaction of the eligibility criteria, study site personnel will call into the IWRS and obtain permission to randomize the subject. The IWRS will determine which drug package for the site to administer to the subject based on a randomization schedule where each treatment is allocated once using a block size of 4 within each study site. Hence, randomization will be stratified by study site with each study site ending up with whole and/or partial block sizes randomized.

10.3. Analysis Sets

Safety Analysis Set:

All subjects who receive at least one dose of study drug will be included in all analyses of safety data. Such subjects will be analyzed according to the treatment actually received.

Intent to Treat (ITT) Analysis Set:

All subjects who meet the study entry inclusion/exclusion criteria, receive at least one dose of study drug, and have at least one valid week of efficacy assessment data (minimum of 4 days) will be included in the ITT analysis set. Subjects will be analyzed according to the treatment group into which they were randomized. The ITT analysis set will be the primary analysis set for efficacy analysis.

10.4. Procedures for Handling Missing Data

The primary analysis will be based on the observed data where weekly SBMs and CSBMs will be standardized to 7-day frequencies. This amounts to missing days

during the week being imputed with the mean for the non-missing days. A valid week will require at least 4 non-missing diary days. Hence, for the primary analysis, weeks with less than 4 diary days are treated as a non-responder for that week. To further assess the impact of missing weeks on the efficacy analyses, a sensitivity analysis will be carried out by treating weeks with less than 4 diary days as a responder for that week.

The valid week rule will also apply for stool consistency and straining score although it is assumed that if the diary was filled out for frequency of stools, it would also be filled out with respect to these items. However, the average weekly stool consistency and the average weekly straining score will be calculated on the observed number of responses without any standardization. For the purposes of calculating an average, days with no stools reported (i.e., a 0 was recorded for the answer to IVRS question 6) will be scored as 0 for average weekly stool consistency and average weekly straining score.

An endpoint week will be defined as the last valid week during the 12-week treatment period where each weekly efficacy variable was obtained. This amounts to creating an endpoint last observation carried forward such that each subject's endpoint value represents the last experience while receiving study drug.

Otherwise, all other observed data will be used in the analyses.

10.5. Methods of Pooling Data

For the purpose of adjusting for investigator effects in statistical models, investigator sites will be pooled into groups based on geographic region and number of subjects enrolled with an aim for comparable sample sizes among pooled investigator sites. The goal of the pooling strategy will be to avoid less than a minimum number of subjects per pooled investigator site. The size of a pooled investigator site would generally not be larger than the total number of subjects enrolled at the highest enrolling individual investigator site. The pooled investigator sites will be used in all applicable analyses where adjustment for investigator effect is desired.

Based on an average of 6 subjects per site to be enrolled, the primary pooled investigator site strategy will target 10 pools of approximately 60 subjects each (approximately 30 per treatment group per pooled investigator site). As a sensitivity analysis, a second pooling will have a target of 20 pools of approximately 30 subjects each (approximately 15 per treatment group per pooled investigator site). The actual designation of membership in a pooled investigator site cannot be made until the final enrollment quantities and final number of sites used is completed. The final pooling strategy will be defined before treatment unblinding, and will be provided as an addendum to the SAP. The goals stated above will be adhered to as closely as possible.

10.6. Visit Windows

Daily IVRS diary data are planned for daily collection starting on the day of the Screening visit and continuing until the planned Week 16 (Visit 8 Day 113) RW visit.

Weekly IVRS diary data are planned for each week of the 2-week screening period (when applicable), each week of the 12-week treatment period, and each week of the 4-week RW period.

For all IVRS efficacy data, the date collected will be used to calculate a relative study day (Rel Day). The relative study day will be calculated as the number of days from the day of first dose. The date of the first dose date is Day 1. The preceding day is Day -1, the day before that is Day -2, etc. There is no Day 0.

Actual study periods will be defined as follows for the purposes of the efficacy evaluations:

- Screening/Baseline Period (Rel Days -14 through Day -1): For the average weekly CSBMs, average weekly SBMs, average weekly stool consistency, average weekly straining score, and average weekly abdominal symptom score (pain, discomfort, bloating, cramping, and fullness), the most recent 7 days will be used to calculate Week -1 values (i.e., days -1 through -7) and remaining days will be used for Week -2 calculations (i.e., day -8 through -14 or more if applicable). The baseline for these variables will then be based on the average of the week -2 and week -1 values. While the screening period may vary somewhat from 14 days, it will generally be required that subjects provide two weekly ratings of the weekly IVRS diary questions during this period.

    - Treatment Period:
        - Week 1 (Rel Day 1-7)
        - Week 2 (Rel Day 8-14),
        - Week 3 (Rel Day 15-21),
        - Week 4 (Rel Day 22-28),
        - Week 5 (Rel Day 29-35),
        - Week 6 (Rel Day 36-42),
        - Week 7 (Rel Day 43-49),
        - Week 8 (Rel Day 50-56),
        - Week 9 (Rel Day 57-63),
        - Week 10 (Rel Day 64-70),
        - Week 11 (Rel Day 70-77), and
        - Week 12 (Rel Day 78-84).

    The week during which the day of the last dose occurs will be considered the last valid week during the 12-week treatment period, assuming it contains at least 4 valid daily IVRS diary days. Otherwise, the last valid week will be the preceding week. The last valid week during the 12-week treatment period will be used as the endpoint week for weekly efficacy summaries.

Only data captured from the first dose until the last dose will be used to derive the weeks during the 12-week treatment period,

• RW Period:
  - Week 1 (Rel Day 1-7 after Randomization #2),
  - Week 2 (Rel Day 8-14 after Randomization #2),
  - Week 3 (Rel Day 15-21 after Randomization #2), and
  - Week 4 (Rel Day 22-28 after Randomization #2).

All data listings will contain a relative study day, regardless of whether the data was collected via IVRS diary or eCRF.

10.7. Statistical Analyses

Summary tabulations will be presented that will display descriptive statistics for each treatment group. The number of observations, mean, standard deviation, minimum, median, and maximum values will be displayed for continuous variables, and the number and percent of subjects per category will be displayed for categorical data. For subject disposition, demographic and baseline characteristics, medical history, gastrointestinal disease history, and prior medications, an overall column (i.e., all subjects combined) will be included.

Statistical analyses will be performed at the two-sided significance level of 0.050 according to the testing procedure described below. The testing procedure will preserve the experiment wise Type I error rate at 5%. All secondary p-values will be considered descriptive.

10.7.1 Subject Disposition

Subject disposition information will be summarized by treatment group and overall. The number and percent of subjects who are randomized, who took a dose of study drug, who complete the study, and who withdraw early from the study will be presented. The primary reason for early withdrawal will also be tabulated. The number of subjects randomized will be used as the denominator for the percentage calculation. Subject disposition, inclusion / exclusion criteria, and protocol deviations will be listed.

The number and percent of subjects in each analysis set will also be tabulated.

10.7.2 Demographic and Background Characteristics

The treatment groups will be descriptively assessed for comparability of demographic and baseline characteristics. Variables included in this assessment will be the demographic characteristics of age at informed consent (years), gender, race, ethnicity, body weight (kg), and BMI (kg/m^2). Screening values (week -1, week -2) and baseline values (average of week -1 and week -2) for average weekly CSBMs, average weekly SBMs, average weekly stool consistency, average weekly straining

score, and average weekly abdominal symptoms of pain, discomfort, bloating, fullness, and cramping will also be summarized for each treatment group and overall.

Weekly ratings of IBS severity and constipation severity will also be summarized for each of the 2 weeks of the screening period. Both categorical and continuous descriptive statistics will be used for the weekly ratings.

Medical history and gastrointestinal (GI) history will be summarized for the number and percentage of subjects for each body system by treatment group and overall. Medical history includes verbatim terms recorded for the subjects. GI history includes duration (years) since IBS symptoms began before randomization, duration (months) since last colonoscopy before randomization, and whether colonoscopy findings are not significant. A summary table will be presented for each analysis set. Medical and GI history will also be listed.

10.7.3 Prior/Concomitant Medication

All prior and concomitant medications administered during the study will be coded using the latest available version of the World Health Organization (WHO) Drug Reference List. The number and percentage of subjects taking prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred name by treatment group and overall. A listing of all medications will be provided.

10.7.4 Study Drug Exposure and Compliance

Days of exposure to study drug will be summarized with descriptive statistics by treatment group for each of the analysis sets. Summary statistics will also be presented for percent compliance to study drug by treatment group for each of the analysis sets. The percent compliance to study drug will be calculated as the total number of tablets dispensed minus the total number of tablets returned divided by two, times the number of days during the treatment period, then multiplied by 100.

10.7.5 Efficacy Variables

Efficacy variables in this trial will be captured via the IVRS on a daily basis (CSBM frequency, SBM frequency, consistency, straining, and abdominal symptoms of pain, discomfort, bloating, fullness, and cramping) or weekly basis (IBS severity, and constipation severity) during the screening (baseline) period, the 12 week treatment period, and the RW period. Adequate relief of IBS symptoms and degree of relief of IBS symptoms will be collected weekly during the treatment period and RW period. The IBS-QOL will be collected by the eCRF prior to and at the end of the treatment period as well as the end of the RW period. Treatment satisfaction will be recorded at the end of each month during the treatment period and the end of the RW period. Use of rescue medication is also collected daily throughout the screening, treatment, and RW periods. Rescue medication usage is incorporated into the derivation of the efficacy variables but is not itself considered an efficacy variable.

The primary efficacy variable will be the overall responder rate. An overall responder will be defined as a weekly responder for 6/12 weeks where both CSBM and

abdominal pain response criteria were met for the week. The CSBM and abdominal pain response criteria are defined below. The weekly overall responder rates will be summarized for each week of the treatment period and the RW period.

The CSBM response criteria is defined as an increase of one or more change in average weekly CSBMs from baseline. The definition of a CSBM is as follows: A CSBM is a SBM for which the subject responds "yes" to the following question; "Did you feel like you completely emptied your bowels?" Any SBM which is preceded within 24 hours by the use of rescue medication will not be counted as a SBM and therefore also not counted as a CSBM as defined above. Should a subject not have data reported for a given week (either due to a gap in reporting or due to discontinuation), the subject will be considered to be a non-responder for the week.

A key secondary efficacy variable will be the overall CSBM responder rate. An overall CSBM responder will be defined as a weekly CSBM responder for 6/12 weeks where the CSBM response criteria were met for the week.

The average weekly CSBMs will be calculated as the sum of the number of CSBMs reported during each day of the defined weekly period divided by the number of days CSBMs were reported times 7. A valid week will require at least 4 days of SBM reporting. The average weekly CSBMs and change from baseline (where baseline is the average of the 2-weeks during the screening period) for each week of the treatment period and 4-week RW period will be summarized. Baseline for the 4-week RW period will be the last week of the treatment period.

The abdominal pain response criteria is defined as a decrease of 30% or more of percent change from baseline in average weekly worst abdominal pain. Abdominal pain will be scored daily using the scale 0 = No pain to 10 = very severe pain. The average weekly abdominal pain score will be calculated as the average score for all days during a valid week. Should a subject not have data reported for a given week (either due to a gap in reporting or due to discontinuation), the subject will be considered to be a non-responder for the week. The average weekly abdominal pain score and percent change from baseline (where baseline is the average of the 2-weeks during the screening period) for each week of the treatment period and 4-week RW period will be summarized. Baseline for the 4-week RW period will be the last week of the treatment period.

A key secondary efficacy variable will be the overall abdominal pain responder rate. An overall abdominal pain responder will be defined as a weekly abdominal pain responder for 6/12 weeks where the abdominal pain response criteria were met for the week.

Additional key secondary efficacy variables consist of the overall responder rate, overall CSBM responder rate, and overall abdominal pain responder rate calculated using a 9/12 week response criteria. Hence, for 9 out of the 12 weeks during the treatment period, the subject met the responder criteria for the 6/12 week responder rates. In addition, for the 9/12 week CSBM responder criteria, it is also required that the average weekly CSBMs for the week are ≥3. A third set of key secondary efficacy variables consist of the durable overall responder rate, durable overall CSBM

responder rate, and durable overall abdominal pain responder rate. The durable responder rates use the same 9/12 week response criteria and in addition, require the last 3/4 weeks of the treatment period to meet the response criteria.

For each of the three sets of efficacy variables described above (i.e., 6/12, 9/12, and durable responders), several sensitivity analyses will be done. Instead of assuming non-response for missing weeks or weeks with less than 4 days of valid diary data, a sensitivity analysis will be carried out imputing response for these weeks. Similarly, instead of assuming a 30% reduction for percent change from baseline in abdominal pain, these analyses will be repeated using a 40% reduction and a 50% reduction as response criteria. Note that for these last 2 analyses, the CSBM responder analyses will not be repeated, only the overall and abdominal pain responder rates.

Secondary efficacy variables will include the following:

The proportion of subjects with ≥ 3 CSBMs per week will be summarized for the baseline, treatment, and RW periods.

Average weekly SBMs will be calculated as described above for average weekly CSBMs. Change from baseline for each week of the 12-week treatment period and 4-week RW period will be summarized using the observed data. Baseline for the 4-week RW period will be the last week of the treatment period.

Subjects will record the consistency of each of their bowel movements on a daily basis through the IVRS utilizing the BSFS scale (Appendix B). The average weekly stool consistency will be calculated as the average score for all valid SBMs during the week. For purposes of calculating an average, days with no stools will be scored a 0. Change from baseline for each week of the 12-week treatment period and 4-week RW period will be summarized using the observed data. Baseline for the 4-week RW period will be the last week of the treatment period.

Straining will be scored for each SBM using the scale 1 = not at all, 2 = a little bit, 3 = a moderate amount, 4 = a great deal, 5 = an extreme amount. The average weekly straining score will be calculated as the average score for all valid SBMs during the week. Change from baseline for each week of the 12-week treatment period and 4-week RW period will be summarized using the observed data. Baseline for the 4-week RW period will be the last week of the treatment period.

Abdominal discomfort, abdominal bloating, abdominal fullness, and abdominal cramping will be scored daily using the 0-10 point scale with 0 representing no presence of the symptom and 10 representing very severe presence of the symptom. The average weekly scores will be calculated as the average score for all days during a valid week. Percent change from baseline for each week of the 12-week treatment period and 4-week RW period will be summarized. In addition, responders at each week (i.e., 30% improvement from baseline) and for 6/12 weeks on treatment will be defined in a similar manner as for abdominal pain responder rates. If no data is present to constitute a valid week, it will be assumed the subject did not respond. Otherwise, observed data will be used to summarize the average weekly abdominal symptom. Baseline for the 4-week RW period will be the last week of the treatment period.

IBS severity and constipation severity will be scored on a weekly basis using the scale 1 = None, 2 = Mild, 3 = Moderate, 4 = Severe, 5 = Very Severe. IBS severity scores and constipation severity scores for each week of the study will be summarized as categorical and continuous data. Observed data will be used for the summaries. Baseline for the 4-week RW period will be the last week of the treatment period.

Adequate relief of IBS symptoms (1 = yes, and 2 = no) will be asked on a weekly basis. The percentage of subjects with adequate relief for each week of the study will be summarized using observed data.

Degree of relief of IBS symptoms will be scored on a weekly basis using 1=completely relieved, 2=considerably relieved, 3=somewhat relieved, 4=unchanged, 5=somewhat worse, 6=considerably worse, 7=as worse as I can imagine. Degree of relief scores for each week of the study will be summarized as categorical and continuous data using observed data.

The IBS-QOL is a validated quality of life tool used for IBS subjects (see Appendix D). Subjects will be asked to complete this assessment a Visit 2 (prior to treatment), Visit 6 (at the end of the 12-week treatment period), and Visit 7 (at the end of the 4-week RW period. The predetermined analysis provided with the tool will be used as described in the user manual. Details will be provided in the SAP. Actual values and change from baseline values for each of the domain scores will be summarized. Baseline for the 4-week RW period will be the last week of the treatment period.

Treatment satisfaction will be recorded by the subject at the end of each month during the treatment period (Visits 4, 5, and 6), and at the end of the RW period (Visit 8). Using the scale: 1= not at all satisfied, 2= a little satisfied, 3= moderately satisfied, 4 =quite satisfied, 5= very satisfied. The treatment satisfaction score will be summarized as a categorical and continuous variable.

The following summarizes the efficacy variables planned for this study:

Table 10-1 Summary of Efficacy Variables and Designation

Variable Designation	Variable name
Primary	6/12 week overall responder rate
Key Secondary	6/12 week overall CSBM responder rate

Key Secondary	6/12 week overall abdominal pain responder rate
Key Secondary	9/12 week overall responder rate
Key Secondary	9/12 week overall CSBM responder rate
Key Secondary	9/12 week overall abdominal pain responder rate
Key Secondary	Durable overall responder rate
Key Secondary	Durable overall CSBM responder rate
Key Secondary	Durable overall abdominal pain responder rate
Sensitivity	6/12 week overall responder rate with imputed responders
Sensitivity	6/12 week overall CSBM responder rate with imputed responders
Sensitivity	6/12 week overall abdominal pain responder rate with imputed responders
Sensitivity	9/12 week overall responder rate with imputed responders
Sensitivity	9/12 week overall CSBM responder rate with imputed responders
Sensitivity	9/12 week overall abdominal pain responder rate with imputed responders
Sensitivity	Durable overall responder rate with imputed responders
Sensitivity	Durable overall CSBM responder rate with imputed responders
Sensitivity	Durable overall abdominal pain responder rate with imputed responders
Sensitivity	6/12 week overall responder rate with 40% change in abdominal pain
Sensitivity	6/12 week overall 40% change in abdominal pain responder rate
Sensitivity	9/12 week overall responder rate with 40% change in abdominal pain
Sensitivity	9/12 week overall 40% change in abdominal pain responder rate
Sensitivity	Durable overall responder rate with 40% change in abdominal pain
Sensitivity	Durable overall 40% change in abdominal pain responder rate
Sensitivity	6/12 week overall responder rate with 50% change in abdominal pain
Sensitivity	6/12 week overall 50% change in abdominal pain responder rate
Sensitivity	9/12 week overall responder rate with 50% change in abdominal pain
Sensitivity	9/12 week overall 50% change in abdominal pain responder rate
Sensitivity	Durable overall responder rate with 50% change in abdominal pain
Sensitivity	Durable overall 50% change in abdominal pain responder rate
Secondary	Weekly overall responder rate
Secondary	Weekly CSBM responder rate
Secondary	Weekly abdominal pain responder rate
Secondary	Weekly proportion of subjects with ≥3 CSBMs per week
Secondary	Average weekly CSBMs
Secondary	Average weekly SBMs
Secondary	Average weekly stool consistency

Secondary	Average weekly straining score
Secondary	Overall abdominal symptom responder rate
Secondary	Weekly abdominal discomfort responder rate
Secondary	Weekly abdominal bloating responder rate
Secondary	Weekly abdominal cramping responder rate
Secondary	Weekly abdominal fullness responder rate
Secondary	Average weekly abdominal pain score
Secondary	Average weekly abdominal discomfort score
Secondary	Average weekly abdominal bloating score
Secondary	Average weekly abdominal cramping score
Secondary	Average weekly abdominal fullness score
Secondary	Weekly IBS severity score
Secondary	Weekly constipation severity score
Secondary	Weekly adequate relief of IBS symptoms
Secondary	Weekly degree of relief of IBS symptoms score
Secondary	IBS-QOL (9 subscales)
Secondary	Treatment satisfaction

10.7.6 Efficacy Analyses

All efficacy variables involving responder rates or proportions will be analyzed using a Cochran-Mantel-Haenszel (CMH) test with pooled investigator site as a stratification (adjustment) variable. Summary statistics will include the pairwise risk difference with placebo along with the asymptotic 95% confidence interval (CI). The adjusted relative risk (adjusted for pooled investigator site) will be based on the ratio of responder rates for placebo versus tenapanor 50 mg BID. The 95% CI versus placebo will also be presented for the adjusted relative risk.

All continuous efficacy variables derived from the daily IVRS questions (i.e., average weekly CSBMs, SBMs, stool consistency, straining score, abdominal symptoms of pain, discomfort, bloating, fullness, and cramping), as well as the weekly IBS severity, constipation severity, and IBS QOL will be analyzed using an analysis of covariance (ANCOVA) model with terms for pooled investigator site, treatment, and baseline as the covariable. Degree of relief of IBS symptoms and treatment satisfaction will be analyzed using an analysis of variance (ANOVA) model with terms for pooled investigator site and treatment.

When the ANCOVA model is implemented, the least square means (LSmeans) will be presented for the actual values and change/percent change from baseline values for each treatment group with the 95% CI. Statistical testing will only be carried out using the change/percent change from baseline since the p-values are the same between the two

analyses. The LSmean difference versus placebo will also be presented with the 95% CI. When the ANOVA model is implemented, all of the above statistics will be presented for the actual values.

A sequential testing procedure will be utilized to control the experiment wise Type I error rate for the primary efficacy variable. Because of the desire to also pre-specify key secondary efficacy variables, the sequential testing procedure will not inflate the overall 5% level. The primary efficacy variable will be tested at the 5% level of significance. If this test is significant, the first key secondary efficacy variable listed in Table 10-1 will be tested at the 5% level. If this test is significant, then the next variable is tested at the 5% level. This procedure continues until one of the tests in the list results in a p-value >5%. Variables up to this point in the list will be declared statistically significant. Interpretation of p-values for the secondary efficacy variables will be descriptive.

In addition to the summaries of the efficacy variables described, figures will be provided depicting the actual means or the change/percent change from baseline for each treatment group at each assessment time. A secondary analysis will also include graphs depicting the cumulative distribution of the percentage reduction of abdominal pain.

10.7.7 Safety Analyses

Safety assessments will be based on the incidence, severity, and type of adverse events, and clinically significant changes in the subject's clinical laboratory tests, vital signs, ECGs and physical examinations.

Adverse events will be coded using the MedDRA adverse event coding system for purposes of summarization. All adverse events reported will be listed in the data listings. Treatment emergent adverse events (TEAEs) will be tabulated, where treatment emergent is defined as any adverse event which occurs after administration of the first dose of study drug and up through the final visit (up to planned Day 113), any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator. TEAEs will also be tabulated by whether events are considered related to treatment (possibly or probably drug-related, or unknown in relationship) and by severity. Serious adverse events and TEAEs resulting in study discontinuation will be tabulated.

Actual values and change from baseline values for clinical laboratory tests will be summarized for each visit collected during the study.The frequency of clinically significant abnormal laboratory test values will be tabulated by treatment group. Shift tables will be derived for changes in laboratory tests from screening to Visit 4, 6, and 8.

Vital signs will be summarized descriptively for actual values and change from baseline values by treatment group and visit. Vital signs are collected at all study visits during the screening period, 12-week treatment period, and 4-week RW period. Baseline for the vital signs will be the average of results obtained during the screening period.

Electrocardiogram results will be summarized descriptively for actual values and change from screening values by treatment group and visit (Screening (Visit 1/Day -14), Week 12 (Visit 6/Day 85), and Week 16 (Visit 8/Day 113)). The overall interpretation will be

summarized with number of subjects and percentages for the normal and abnormal ECG result categories.

All vital signs and electrocardiogram results will be listed. Abnormal or clinically significant results will be flagged.

Physical examinations are collected at Screening (Visit 1/Day -14), Week 12 (Visit 6/Day 85), and Week 16 (Visit 8/Day 113). The number and percentage of subjects in each category will be presented for each visit by treatment group.

All physical examination results will be listed. Abnormal physical exam results will be flagged.

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11. ADMINISTRATIVE REQUIREMENTS

11.1. Good Clinical Practice

The study will be conducted in accordance with the current GCP/ICH Guidelines and relevant regulatory requirement(s). Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki and that the clinical trial data are credible. The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. A Trial Master File will be established at the beginning of the study, maintained for the duration of the trial and retained according to appropriate regulations.

11.2. Ethical Considerations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator Brochure, informed consent, advertisements (if applicable), written information given to the subjects (including subject information material), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

11.3. Subject Informed Consent and Information

Prior to entry in the trial, the Investigator must explain to potential subjects or their legally acceptable representative, the trial and the implications of participation. Subjects will be told that their participation is voluntary and they may withdraw consent to participate at any time. Subjects will be told that competent authorities and authorized Ardelyx personnel, its business partners or its CRO designee may access their records without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF) the subject or legally acceptable representative is authorizing

such access through an authorization meeting the requirements of the Health Insurance Portability and Accountability Act of 1996. Each subject (or their legally authorized representative) that wants to participate in the study must sign and date the ICF (and other locally required documents) after the nature of the study has been fully explained prior to performing any study-related activities. The subject (or their legally acceptable representative) will be given sufficient time to read the ICF and to ask additional questions. After having obtained the consent, a copy of the informed consent document must be given to the subject. In case the subject is unable to read, an impartial witness must attest the informed consent. Subjects who are unable to comprehend the information provided can only be enrolled after consent by a legally acceptable representative.

The consent form that is used must be approved by both the reviewing IRB and by Ardelyx or its CRO designee.

All reports and communications relating to the study will identify subjects by initials and assigned number only. A "Subject Screening Log" that reports on all subjects that were seen to determine eligibility for inclusion in the trial will also be completed by the Investigator.

11.4. Subject Confidentiality

The collection and processing of data from subjects enrolled in this trial will be limited to those data that are necessary to investigate the safety, quality and utility of the investigational product(s) used in this trial. These data will be processed with adequate precautions to ensure confidentiality.

In order to maintain subject/subject privacy, all CRFs, study drug accountability records, study reports and communications will identify the subject by initials and the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from Ardelyx, its designee(s) and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available except to the extent permitted by the applicable laws and regulations.

11.5. Protocol Compliance

The Investigator will conduct the trial in compliance with the protocol provided by Ardelyx, and given approval by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the Investigator and Ardelyx. Changes to the protocol will require written IRB/IEC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval for minor change(s) in ongoing trials that have the approval of the IRB/IEC. Ardelyx will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate

hazard(s) to subjects, the Investigator will contact Ardelyx, if circumstances permit, to discuss the planned course of action

11.6. Study Monitoring and On-site Audits

Monitoring and auditing procedures developed by Ardelyx or its CRO designee will be followed, in order to comply with GCP guidelines. Routine monitoring visits will be made to assure compliance with the study protocol, to review and compare the subject's eCRF with source documents, to ensure adequate records of clinical supplies are maintained and to assess the continued suitability of the investigational site. The Investigator agrees to allow the site monitors, and other authorized personnel or designees, access to the subject's medical records, regulatory binder, study binder, and source documents as needed to assure the conduct of the study was within compliance.

Upon completion of the study the site monitor will make a final assessment of the conduct of the study and inventory all clinical supplies to be returned to Ardelyx. All unused study drug is to be returned to Ardelyx or designee.

Regulatory authorities, the IEC/IRB, and/or Ardelyx's clinical quality assurance group, its CRO designee or business partners may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

11.7. Case Report Form Completion

An Electronic Data Capture (EDC) system will be used for this study. Electronic case report forms (eCRFs) will be accessed for each subject.

eCRFs will be completed for each randomized study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events and subject status.

The Investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

Prior to submission within the EDC system, eCRFs must be reviewed for completeness and accuracy, and electronically signed and dated by the Investigator where indicated.

11.8. Drug Accountability/Retention

Accountability for the study drug at the trial site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate

individual. Drug accountability records indicating the study drug's delivery date to the site, inventory at the site, use by each subject, and return to Ardelyx (or disposal of the drug, if approved by Ardelyx) will be maintained by the clinical site. These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study drug received from Ardelyx. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and subject numbers. Ardelyx or its CRO designee will review drug accountability at the site on an ongoing basis during on-site monitoring visits.

The Investigator acknowledges that the study drug supplies are investigational and as such must be handled strictly in accordance with the protocol and container label. Supplies should be dispensed under the supervision of the Investigator or designee. Study drug will be stored in a limited access area and under the appropriate conditions as specified on delivery.

Unused or partially used bottles of study drug will be stored until the study monitor at the end of the study performs a final inventory. At the completion of this trial, all unused, partially unused, or empty multiple-dose bottles must be returned to Ardelyx, or designee.

11.9. Study Completion or Premature Closure

The Investigator will complete the study and the eCRF in satisfactory compliance with the protocol within approximately 1 week of study completion.

Ardelyx reserves the right to close the investigational site or terminate the trial at any time. Reasons for the closure of an investigational site or termination of a trial by Ardelyx may include:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enter subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, all study materials (completed, partially completed, study drug, etc.) must be returned to Ardelyx.

11.10. Record Retention

All case report forms and all source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses and dates of therapy prior to and during this study, drug dispensing/disposition records) that support case report forms of each subject must be retained in the files of the responsible Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements. The Investigator should take measures to prevent accidental or premature destruction of these records. Under no

circumstances shall the Investigator re-locate or dispose of any trial documents before having obtained Ardelyx written approval. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. Ardelyx must be notified in writing if a custodial change occurs. If it becomes necessary for Ardelyx or a regulatory authority to review any documentation relating to this trial, the Investigator must permit access to such records. Any difficulty in storing original records must be discussed with the study monitor prior to the initiation of the trial.

12. USE OF INFORMATION AND PUBLICATION

All information regarding tenapanor supplied by Ardelyx to the Investigator or generated by the Investigator in accordance with the conduct of the study is privileged and confidential information of Ardelyx. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without written consent from Ardelyx. It is understood that there is an obligation to provide Ardelyx with complete data obtained during the study. The information obtained from the clinical trial will be used by Ardelyx in connection with the development of tenapanor and may be disclosed by Ardelyx to regulatory authority(ies), other Investigators, potential corporate partners, or consultants as required.

The Investigator's right and obligations with respect to publishing or otherwise presenting information regarding the study are detailed in the Publication provisions of the Clinical Study Agreement among the Investigator, the clinical site and Ardelyx. The Investigator shall comply with such provisions.

13. SIGNATURES

13.1. Investigator Signature

I have read Clinical Protocol TEN-01-301, Edition 1, dated 18 August 2015, A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study with a 4-Week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C) and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by Ardelyx or its CRO designee and the Institutional Review Board (IRB) and will fulfill all responsibilities for submitting pertinent information to the IRB responsible for this study.

I further agree that Ardelyx, its designee(s) or its CRO designee shall have access to any source documents from which case report form information may have been generated.

_____

Principal Investigator printed name

_____ _____

Principal Investigator signature Date

_____

_____

_____

Investigational site or name of institution and location (printed)

13.2. Sponsor Signature

This clinical study protocol has been reviewed and approved by Ardelyx, Inc.

[redacted]

[redacted]

Date

14. APPENDIX A: Rome III Criteria for the Diagnosis of IBS

Diagnostic Criteria*

Recurrent abdominal pain or discomfort** at least 3 days per month in the last 3 months associated with 2 or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

**Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation for subject eligibility.

Supportive symptoms that are not part of the diagnostic criteria include abnormal stool frequency ([a] ≤ 3 bowel movements per week or [b] ≥3 bowel movements per day), abnormal stool form ([c] lumpy/hard stool or [d] loose/watery stool), [e] defecation straining, [f] urgency, or also a feeling of incomplete bowel movement, passing mucus, and bloating.

Subtyping IBS by Predominant Stool Pattern is as follows:

- IBS with constipation (IBS-C): hard or lumpy stools[a] ≥25% and loose (mushy) or watery stools[b] <25% of bowel movements
- IBS with diarrhea (IBS-D): loose (mushy) or watery stools[b] ≥25% and hard or lumpy stool[a] <25% of bowel movements.
- Mixed IBS (IBS-M): hard or lumpy stools[a] ≥25% and loose (mushy) or watery stools[b] ≥25% of bowel movements.
- Unsubtyped IBS—insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M[c].

The validity and stability of such subtypes over time is unknown and should be the subject of future research.

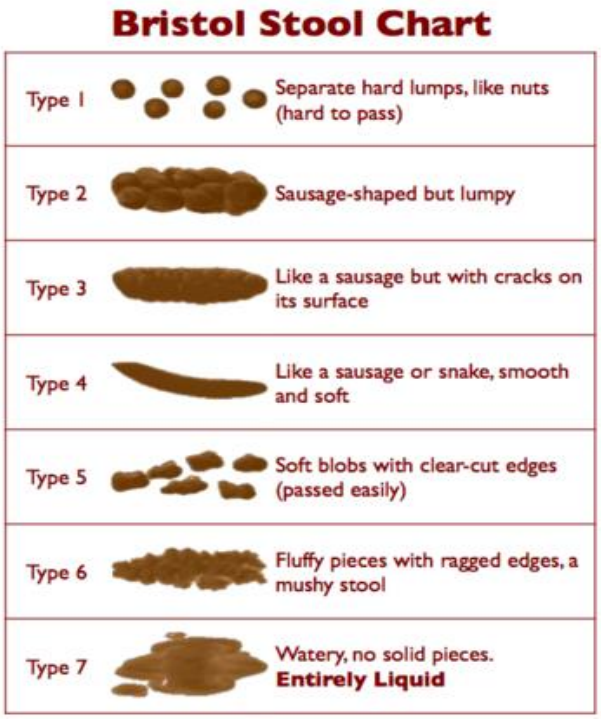
[a]Bristol Stool Form Scale 1–2 (separate hard lumps like nuts [difficult to pass] or sausage shaped but lumpy).

[b]Bristol Stool Form Scale 6–7 (fluffy pieces with ragged edges, a mushy stool or watery, no solid pieces, entirely liquid).

[c]In the absence of use of antidiarrheals or laxatives

Longstreth, GF, Thompson, WG, Chey, WD, Houghton, LA, Mearin, F, and Spiller, RC. Functional Bowel Disorders. Gastroenterol. 2006;130:1480–1491.

15. APPENDIX B: Bristol Stool Form Scale (BSFS)



Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand. J. Gastroenterol. 1997;32(9):920–924.

16. APPENDIX C: Clinical Laboratory Tests

- **Serum Chemistry**

  Albumin
  Alkaline Phosphatase
  ALT
  AST
  Bicarb/CO_2
  Total Bilirubin
  Direct Bilirubin
  Indirect Bilirubin
  Calcium
  Chloride
  Total Cholesterol
  Creatinine
  Glucose
  Inorganic Phosphorous
  LDH
  Potassium
  Total Protein
  Sodium
  Triglycerides
  BUN/Urea
  Uric Acid

- **Hematology**

  WBC count
  RBC
  RBC Indices
    MCV
    MCH
    MCHC
  Hemoglobin
  Hematocrit
  Differential:
    Bands
    Monophils
    Neutrophils
    Eosinophils
    Lymphocytes
    Basophils
    Platelet Count

- **Urinalysis**

  Urine β-hCG
  Appearance
  Specific Gravity
  pH
  Protein
  Glucose
  Ketones
  Blood
  Nitrite
  Microscopic

- **Serology**

  HIV
  Hepatitis B
  Hepatitis C

- **FSH**

17. APPENDIX D: Irritable Bowel Syndrome – Quality of Life Questionnaire (IBS-QOL)

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

Pages 66 through 73

PLEASE WRITE IN
TODAY'S DATE: _____ _____ _____
MONTH DAY YEAR

PARTICIPANT ID:

PLEASE READ THIS CAREFULLY

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

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

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

YOUR RESPONSES WILL BE KEPT STRICTLY CONFIDENTIAL.

IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT:

SITE ADDRESS AND PHONE NUMBER TO BE PLACED HERE

IBS-QOL Original US English 2002

IBS-QOL - United States/English
IBS-QOL_AU1.0_eng-USori

About how you feel

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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