16.1 Study Information

16.1.1 Protocol and protocol amendments

The following documents are included:

- Final protocol, dated 29 Jan 2016.

CLINICAL STUDY PROTOCOL

Protocol No. TEN-01-303

An Open Label Long-Term Safety Study of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C)

29 January 2016
Edition No. 1

SPONSOR:

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

PROTOCOL SUMMARY

Study Title	An Open Label Long-Term Safety Study of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C)
Sponsor	Ardelyx, Inc.
Study Phase	3
Treatment Groups	Single treatment group; approximately 300 subjects total
No. of Sites	Approximately 50-60
Dose Form and Frequency	Tablet(s) Twice daily (BID)
Doses	Tenapanor 50 mg BID (total daily dose 100 mg)
Methodology	This is an open label study to evaluate the safety of tenapanor 50 mg BID in subjects with IBS-C (Rome III criteria). Subjects who have completed either the TEN-01-301 (16 weeks) or TEN-01-302 (26 weeks) studies may be enrolled. Subjects will take tenapanor for up to 52 weeks total based on previous protocol and this study.
Duration	For each subject, the entire exposure to tenapanor will last for a total of approximately 52 to 55 weeks; including completion of either the TEN-01-301 or TEN-01-302 studies. For subjects completing studies TEN-01-301 or TEN-01-302, TEN-01-303 treatment duration will be 39 and 26 weeks, respectively.

Treatment Period	During the treatment period of up to 39-weeks subjects will return for study visits approximately every 13 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.
Inclusion/Exclusion Criteria	**Inclusion Criteria** Subjects meeting all of the following inclusion criteria will be eligible for enrollment: 1. Subjects completed all 16 weeks of TEN-01-301 or all 26 weeks of TEN-01-302. 2. In the opinion of the investigator, the subject demonstrated adequate compliance with the study procedures during either the TEN-01-301 or TEN-01-302 studies preceding this long term safety study. 3. 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) as determined in either TEN-01-301 or TEN-01-302 studies. If of child-bearing potential, must have negative pregnancy test at last visit for TEN-01-301 or TEN-01-302 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 study, or • Double barrier method, • Sterilization of one or both partner(s). 4. Males must agree to use an appropriate method of barrier contraception (e.g., latex condom with a spermicidal agent) or have documented surgical sterilization

	5. The subject has signed the informed consent and is willing to comply with all trial visits and assessments **Exclusion Criteria** Subjects meeting one or more of the following exclusion criteria are not to be enrolled in the study: 1. The subject has been withdrawn or discontinued prematurely from either TEN-01-301 or TEN-01-302 2. The subject reports using any prohibited medication and is not willing to abide by the restrictions for intake 3. Pregnant or lactating women. 4. 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.
Statistical Considerations	Summary tabulations will be presented that will display descriptive statistics at each visit for each treatment cohort and for all subjects in the safety analysis set. 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 receive at least one dose of study drug will be included in all analyses of safety. Safety analyses will include summaries for treatment emergent adverse events, clinical laboratory tests, vital signs, 12-lead ECGs, and physical exams. Study drug exposure, compliance and concomitant medications will also be summarized.

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1. LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransaminase
AST	Aspartate aminotransaminase
BM	Bowel movement
BMI	Body mass index
BSFS	Bristol stool form scale
BUN	Blood urea nitrogen
CIC	Chronic idiopathic constipation
CKD	Chronic kidney disease
CO_2	Carbon dioxide
CRC	Child resistant closure
CRF	Case report form;
CRO	Contract research organization
CSBM	Complete spontaneous bowel movement
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
GI	Gastrointestinal
H+	Hydrogen
HDPE	High density polyethylene
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

IRB	Institutional review board
ITT	Intent to treat
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
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
OBD	Opioid bowel dysfunction
QA	Quality assurance
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SBM	Spontaneous bowel movement
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event
WBC	White blood cell count
WHO	World health organization

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 open label long-term safety study will evaluate the safety of tenapanor in subjects with constipation predominant IBS (IBS-C) who have completed either study TEN-01-301 (16 weeks) or TEN-01-302 (26 weeks). Subjects who qualify will receive tenapanor 50 mg BID for up to 52 weeks total based on previous protocols and this study. For subjects completing studies TEN-01-301 or TEN-01-302, treatment duration will be 39 and 26 weeks, respectively.

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 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 $C_{50}H_{68}Cl_{l6}N_8O_{10}S_2$.

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.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to assess the safety of tenapanor 50 mg for the treatment of IBS-C when administered twice daily (BID) for up to 52 weeks.

4. INVESTIGATIONAL PLAN

This is an open label long-term safety study of tenapanor in subjects with IBS-C. Subjects who have completed either study TEN-01-301 or TEN-01-302 will be eligible to enroll in this study.

During the open label treatment period, subjects will return for study visits approximately every 13 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.

5. STUDY POPULATION

5.1. General Considerations

Approximately three-hundred (300) subjects who have completed TEN-01-301 or TEN-01-302 and meet all of the inclusion criteria, and none of the exclusion criteria will be enrolled into the study at approximately 50 to 60 US clinical centers.

5.2. Inclusion Criteria

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

1. Subjects completed all 16 weeks of TEN-01-301 or all 26 weeks of TEN-01-302.
2. In the opinion of the investigator, the subject demonstrated adequate compliance with the study procedures during either TEN-01-301 or TEN-01-302 studies preceding this long term safety study.
3. 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) as determined in either TEN-01-301 or TEN-01-302 studies. If of child-bearing potential, must have negative pregnancy test at last visit for TEN-01-301 or TEN-01-302 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 study, or
   - Double barrier method,
   - Sterilization of one or both partner(s).
4. Males must agree to use an appropriate method of barrier contraception (e.g., latex condom with a spermicidal agent) or have documented surgical sterilization
5. The subject has signed the informed consent and is willing to comply with all trial visits and assessments

5.3. Exclusion Criteria

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

1. The subject has been withdrawn or discontinued prematurely from either TEN-01-301 or TEN-01-302

2. The subject reports using any prohibited medication and is not willing to abide by the restrictions for intake
3. Pregnant or lactating women.
4. 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..

5.4. Rescue Medication

Rescue medications are allowed for severe constipation (i.e, at least 72 hours after the subject's previous BM or when symptoms become intolerable). Bisacodyl (5 mg tablet or 10 mg suppository) is the preferred rescue medication; however, other rescue medications prescribed by a physician as standard of care are allowed.

5.5. Prohibited Concurrent Medications

The following medications are specifically prohibited from use during the study, unless specified as a rescue medication.

All prescription and/or over the counter medications used to treat constipation and/or IBS-C (e.g., linzess, amitiza, miralax, dulcolax, lactulose, bisacodyl).

Narcotics either alone or in combination (e.g., tramadol, codeine, morphine, propoxyphene, loperamide, diphenoxylate, paregoric) if they are being used chronically and are expected to be taken indefinitely in the future.

Patient is planning to receive an investigational drug (other than study drug) or investigational device at any time during this study (any investigational or imported drugs that have not been approved for human use by the FDA)

5.6. Removal of Subjects from Therapy or Assessment

Subjects will be discontinued from the study if a subject experiences a study drug related serious adverse event.

Subjects will be informed that they can 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 4 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.

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.

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) tenapanor 50 mg tablets.

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

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). All eligible subjects will receive tenapanor 50 mg BID. Subjects will take one tenapanor tablet twice daily, immediately prior to breakfast or the first meal of the day and immediately prior to dinner.

Subjects will receive three bottles of drug at Visit 1 (Day 1) and Visit 2 (Week 13 ± 2). If the subject was previously in study TEN-01-301, they will also receive three bottles of drug at Visit 3 (Week 26 ± 2). At each visit the subject will be asked to return their unused drug and bottles. Study drug compliance will be monitored by the clinical site staff and will be verified by the study monitor during on-site monitoring visits.

6.4. Randomization and Blinding

This is an open label study. There is no randomization and all subjects and study personnel are unblinded. All subjects that enroll in this study will receive tenapanor 50 mg BID.

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. In addition, a telephone contact will take place as footnoted below to find out if any treatment related problems have occurred. Additional telephone calls to the subjects for treatment follow-ups of AEs will be made as needed.

Evaluation	**Enroll[a]**	**Treatment Period[e]**		
Site Visit[h]	**1**	**2**	**3[b]**	**4/ET[c]**
Study Week(s)	**1**	**13±2**	**26±2**	**39±2**
Informed Consent[a]	X			
Inclusion/Exclusion	X			
Concurrent Medications		X	X[b#]	X
Physical Exam			X[b]	X
Vital Signs[d]		X	X[b#]	X
Safety Laboratories[f]			X[b]	X
Urine Pregnancy test[fg]		X	X[b]	X
Urinalysis[f]			X[b]	X
12-lead electronic ECG			X[b]	X
Drug Dispensed/returned	D	D/R	D[#]/R[b#]	R
Adverse Event Assessments		X	X[b#]	X

[a]The Informed Consent Form (ICF) must be signed before any protocol procedures are performed.
[b]This is the final visit for subjects that enrolled from Protocol TEN-01-302 and only procedures with this footnote are performed on subjects from TEN-01-302. Procedures for subjects enrolled from Protocol TEN-01-301 are marked with a #
[c]This is the final visit for subjects that enrolled from Protocol TEN-01-301. It is also used as an early termination (ET) visit.
[d]Vital signs include systolic and diastolic blood pressure (seated), heart rate, respiratory rate, temperature and body weight.
[e]When a subject discontinues early, procedures performed at Visit 4 should be performed at the subject's last visit.
[f]Laboratory assessments are detailed in Appendix A
[g] If the urine pregnancy test is positive, it will be confirmed with a serum pregnancy test.
[h]Telephone calls will be made to subjects monthly during the two months prior to a site visit to ascertain if there have been any treatment related problems (Weeks 5±1, 9±1, 17±1, 22±1 for subjects from TEN-01-301 and TEN-01-302 and for subjects from TEN-01-301 also Weeks 30±1 and 35±1).

8. STUDY EVALUATIONS

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

8.1. Evaluations and procedures at Visit 1 (Day 1)

The following procedures will be conducted at Visit 1:

- Informed Consent
- Inclusion/Exclusion Criteria
- Drug Dispensed

8.1.1 Telephone contacts (Weeks 5±1, 9±1, 17±1, 22±1, for subjects from TEN-01-301 also Weeks 30±1 and 35±1)

- Concurrent Medications (changes since last visit)
- Adverse Events

8.1.2 Evaluations and procedures at Visit 2 (Week 13 ±2)

- Concurrent Medications (changes since last visit)
- Vital signs
- Urine Pregnancy test
- Adverse Events
- Drug Returned
- Drug Dispensed

8.1.3 Evaluations and procedures at Visit 3 (Week 26 ±2)

This is the end of treatment visit for those subjects from study TEN-01-302

- Concurrent Medications (changes since last visit)
- Vital Signs
- Physical Exam (only TEN-01-302 subjects)
- Serum Chemistry and Hematology (only TEN-01-302 subjects)
- Urine Pregnancy Test
- Urinalysis (only TEN-01-302 subjects)
- ECG (only TEN-01-302 subjects)

- Adverse Events
- Drug Returned
- Drug Dispensed (only TEN-01-301 subjects)

8.1.4 Evaluations and procedures at Visit 4 (Week 39 ±2)

This is the end of treatment visit for those subjects from study TEN-01-301

- Concurrent Medications (changes since last visit)
- Vital Signs
- Physical Exam
- Serum Chemistry and Hematology
- Urine Pregnancy Test
- Urinalysis
- ECG
- Adverse Events
- Drug Returned

8.2. Safety Assessments

8.2.1 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.

8.2.1.1 Adverse events

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

8.2.1.2 Physical examination

A complete physical examination will be conducted during either Visit 3 (TEN-01-302) or Visit 4 (TEN-01-301) (and at any early termination visit).

8.2.1.3 Electrocardiogram

A 12-lead electrocardiogram will be obtained during either Visit 3 (TEN-01-302) or Visit 4 (TEN-01-301) (and at any early termination visit).

8.2.1.4 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 Visits 2, 3 and 4 (subjects from TEN-01-301 and early terminations only).

8.2.1.5 Clinical laboratory tests

A central laboratory will perform clinical laboratory tests. Blood samples will be drawn from subjects for serum chemistries and hematology at either Visit 3 (TEN-01-302) or Visit 4 (TEN-01-301) (and at any early termination visit). Urine will be taken for urinalysis at either Visit 3 (TEN-01-302) or Visit 4 (TEN-01-301) (and at any early termination visit). A urine pregnancy test will be performed at Visits 2, 3 and 4 (TEN-01-301 only). If the urine pregnancy test is positive, it will be confirmed with a serum pregnancy test. See Appendix A for specific laboratory tests.

Clinical laboratory test values that are considered abnormal will be noted as clinically significant or not 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.

8.3. Total Blood Volume Required for Study

Table 8-1 Approximate Blood Volume per Subject

Test	Number of Samples	Volume (mL)	Total (mL)
Hematology (blood)	1	3	3
Chemistry (serum)	1	7	7
Total	**2**	**--**	**10**

8.4. 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. 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) are 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 (Enrollment) and the final visit (up to Weeks 26 or 39, Visits 3 or 4).

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 hours 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

Ardelyx will assume responsibility for appropriate reporting of adverse events to regulatory authorities. Ardelyx will report Suspected Unexpected Serious Adverse Reactions (SUSARs) to all investigational sites.

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 (either Visit 3 (TEN-01-302) or Visit 4 (TEN-01-301)). 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 open label long-term safety study will evaluate the safety of tenapanor in subjects with constipation predominant IBS (IBS-C) who have completed either study TEN-01-301 or TEN-01-302. Approximately, 300 subjects who qualify will be enrolled at approximately 50-60 US clinical centers and receive tenapanor 50 mg BID for up to 52 weeks total (previous protocol and this study).

. A statistical analysis plan (SAP) will be developed, finalized, and signed-off on prior to the database lock. 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 analyses. 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

Based on the two Phase 3 studies (TEN-01-301 and TEN-01-302) and the different treatment arms, 300 subjects entered into this open label long-term safety study should produce approximately 150 subjects with at least 52 weeks exposure to tenapanor 50 mg BID and an additional 150 subjects with 26 to 39 weeks of exposure to tenapanor 50 mg BID.

10.2. Randomization and Stratification

This is an open-label study. All subjects will receive tenapanor 50 mg BID.

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.

10.4. Procedures for Handling Missing Data

The safety analysis will be based on the observed data. No imputations or carried forward analyses will be done.

10.5. Methods of Pooling Data

No data will be pooled for purposes of analyses.

10.6. Visit Windows

Observed data will be used for the safety analyses. No visit windows will be applied.

10.7. Statistical Analyses

Summary tabulations will be presented that will display descriptive statistics by visit for four treatment cohorts and for all subjects in the safety analysis set. These cohorts are identified below.

Table 10-1 Treatment Cohorts for Summary Tabulations

	Protocol 301		Protocol 303
Cohort	12-weeks	4-weeks	39-weeks
1	Tenapanor 50 mg BID	Tenapanor 50 mg BID	Tenapanor 50 mg BID
2	Tenapanor 50 mg BID	Placebo	Tenapanor 50 mg BID
3	Placebo	Tenapanor 50 mg BID	Tenapanor 50 mg BID
	Protocol 302		
	26-weeks		26-weeks
4	Tenapanor 50 mg BID		Tenapanor 50 mg BID
5	Placebo		Tenapanor 50 mg BID

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.

As this is an open label study of only treatment with tenapanor 50 mg BID, no statistical testing will be done.

10.7.1 Subject Disposition

Subject disposition information will be summarized by treatment cohort and all subjects overall. The number and percent of subjects who are enrolled, 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 enrolled 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 the safety analysis set will also be tabulated.

10.7.2 Demographic and Background Characteristics

Demographic and background characteristics from TEN-01-301 and TEN-01-302 will be summarized by treatment cohort and all subjects overall. 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).

Medical history and gastrointestinal (GI) history from TEN-01-301 and TEN-01-302 will be summarized for the number and percentage of subjects for each body system. Medical history includes verbatim terms recorded for the subjects. GI history includes duration (years) since IBS symptoms began before enrollment, duration (months) since last colonoscopy before enrollment, and whether colonoscopy findings are not significant. Medical and GI history will also be listed.

10.7.3 Prior/Concomitant Medication

All medications administered during this study will be considered concomitant. These medications will be coded using the latest available version of the World Health

Organization (WHO) Drug Reference List. The number and percentage of subjects taking concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred name by treatment cohort and all subjects 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 cohort and all subjects overall. Summary statistics will also be presented for percent compliance to study drug. 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 treatment, then multiplied by 100.

10.7.5 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 for each treatment cohort and overall, 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 (Visit 3 for subjects from TEN-01-302 and Visit 4 for subjects from TEN-01-301), 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 (including urinalysis) will be summarized at each visit collected during the study for each treatment cohort and overall. The frequency of clinically significant abnormal laboratory test values will be tabulated by treatment cohort and overall. Shift tables will be derived for changes in laboratory tests from the last values obtained during TEN-01-301 or TEN-01-302 to Visit 3 or 4.

Vital signs will be summarized descriptively for actual values and change from baseline values by visit and treatment cohort as well as overall. Vital signs are collected at study visits 2, 3 and 4, as applicable. Baseline for the vital signs will be the last values obtained during TEN-01-301 or TEN-01-302.

12-lead electrocardiogram (ECG) results will be summarized descriptively for actual values and change from baseline values by treatment cohort and overall for each visit (Visit 3 or Visit 4 as applicable). Baseline for the ECG will be the last values obtained during TEN-01-301 or TEN-01-302. 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 Visit 3 and Visit 4, as applicable. The number and percentage of subjects in each category will be presented for each visit by treatment cohort and overall.

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

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 screened and 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 consent for 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 written approval from Ardelyx. 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-01-303, Edition 1, dated 29 January 2016, An Open Label Long Term Safety Study to Evaluate the 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

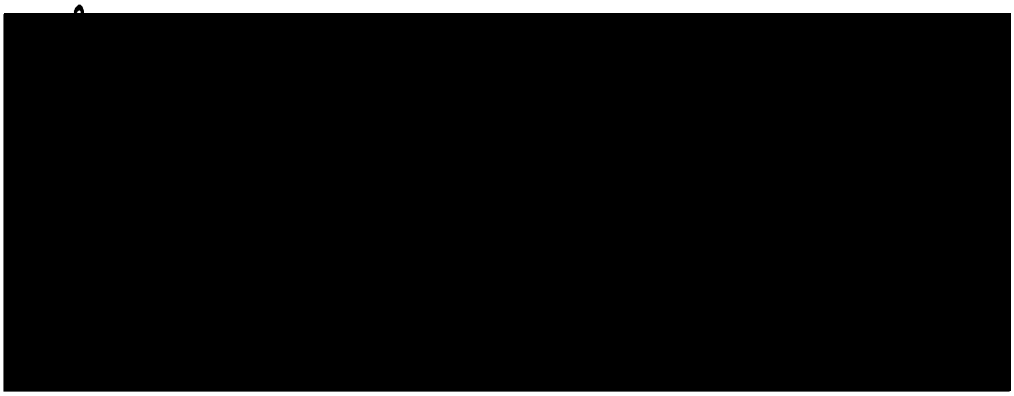
_____

_____

_____

Investigational site or name of institution and location (printed)

13.2. Sponsor Signature



14. APPENDIX A: 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

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NOTE TO FILE

Protocol No. TEN-01-303

An Open Label Long-Term Safety Study of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C)

29 January 2016
Edition No. 1

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11 March 2016

There is an administrative/clerical error on page 32 of the protocol, Section 13.1, Investigator Signature. The protocol title is written as follows:

An Open Label Long Term Safety Study to Evaluate the Safety of Tenapanor for the Treatment of Constipation-Predominant Irritable Bowel Syndrome (IBS-C).

The underlined portion "to Evaluate the Safety" was added in error.

[redacted]