16.1.9 Documentation of statistical methods

The following documents are included:

- Final Statistical Analysis Plan, dated 08 Mar 2016

STATISTICAL ANALYSIS PLAN

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

Investigational Product:	Tenapanor
Protocol Number:	TEN-01-303
Development Phase:	Phase 3
Sponsor:	Ardelyx, Inc. 34175 Ardenwood Blvd. Fremont, CA 94555

SAP Version V1.1 Final

SAP Date: 8 March 2016

Original Protocol: 29 January 2016

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SIGNATURE PAGE

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

We, the undersigned, have reviewed and approved this statistical analysis plan.

[redacted]

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse event
ATC	Anatomical therapeutic chemical
BID	twice per day
BMI	Body mass index
ECG	12-Lead Electrocardiogram
GI	Gastrointestinal
HEENT	Head, ears, eyes, nose, and throat
IBS	Irritable bowel syndrome
IBS-C	Constipation-predominant irritable bowel syndrome
ICF	Informed consent form
n, N	Number of subjects with observations or number of subjects in an analysis set
PR	ECG interval
PT	Preferred term
QRS	Principal deflection in ECG
QT	ECG interval
QT_c	QT interval which has been corrected by taking into account heart rate
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This document provides a description of the statistical methods and procedures to be implemented for the analyses of data from the Ardelyx, Inc. study with protocol number TEN-01-303. No deviations from this Statistical Analysis Plan (SAP) are anticipated. However, if any deviations occur, they will be documented in the final clinical study report. No deviation from the primary analyses will be considered.

2. STUDY CHARACTERISTICS

2.1 Primary Objective

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

This SAP will address the primary objective for this study. If other objectives are identified or the usage of the data collected for the purposes of this study change, these objectives will be addressed at a later time through a separate analysis plan and/or report.

2.2 Study Design and Duration

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, 12-lead electrocardiogram (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.

2.2.1 Treatments 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.

2.2.2 Randomization and Blinding

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

2.2.3 Duration of Study

For each subject, the entire study 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. The study flow chart, including all procedures to be performed during the study is presented below.

SCHEDULE OF ASSESSMENTS FOR THE STUDY

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**		
Site Visit[h]	**1**	**2**	**3[b]**	**4/ET[c]**
Study Week	**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
Clinical Laboratory Tests[f]			X[b]	X
Urine Pregnancy test[fg]		X	X[b#]	X
Urinalysis[f]			X[b]	X
12-lead 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 who enrolled from Protocol TEN-01-302 and only procedures with this footnote are performed. Procedures for subjects enrolled from Protocol TEN-01-301 are marked with a #.
[c] This is the final visit for subjects who enrolled from Protocol TEN-01-301.
[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 of the protocol.
[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).

2.3 Safety Variables

Safety variables will include adverse event (AE) reporting throughout the trial, clinical laboratory tests (serum chemistry, hematology, and urinalysis), vital signs (including body weight body mass index [BMI]), 12-lead ECGs, and physical examinations.

3. STATISTICAL METHODOLOGY

3.1 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.

3.2 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.

3.3 Procedures for Handling Missing Data

The safety analysis will be based on the observed data. Except for provisions for estimating the date of the last dose (Section 3.6.4), no imputations or carried forward analyses will be performed.

3.4 Methods of Pooling Data

Other than the treatment cohorts described below, no data will be pooled for purposes of analyses.

3.5 Visit Windows

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

3.6 Statistical Analyses

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

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 performed.

3.6.1 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.

3.6.2 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.

3.6.3 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 including the reported term, preferred name, ATC class, start and stop dates, and other relevant data will be provided.

3.6.4 Study Drug Exposure and Compliance

Days of exposure to study drug will be summarized with descriptive statistics by treatment cohort and all subjects overall. In addition, a contingency table will be provided to display the number and percentage of subjects in each treatment cohort and overall with exposure in the following categories: ≤13 weeks, >13 to ≤26 weeks, and >26 weeks.

Days of possible exposure is defined as:

date of last dose of study drug – date of first dose of study drug + 1.

When the last known dose date is missing, the last known clinic visit date during the treatment period will be used, and the plus 1 will be removed from the calculation.

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 the treatment period, then multiplied by 100.

Summary statistics will be presented for percent compliance to study drug by treatment cohort and overall. The count and percentage of subjects with overall compliance <80%, 80%-100%, and >100% will also be tabulated by treatment cohort and overall.

3.7 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.

3.7.1 Adverse Events

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. A treatment-emergent AE (TEAE) is any AE that starts on or after the first dose of study drug 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, or any event which occurs prior to the first dose of study drug and worsens in severity or is

subsequently considered drug-related by the investigator. An AE is considered drug related if it is possibly related or probably related to study drug.

TEAEs will also be tabulated by whether events are considered related to treatment and by severe severity. Serious adverse events (SAEs) and TEAEs resulting in study discontinuation will be tabulated.

Summarization of AEs will include subject incidence of the following:

- All TEAEs
- Drug-related TEAEs
- Severe TEAEs
- Severe and drug-related TEAEs
- SAEs
- Drug-related SAEs
- Death due to AEs
- TEAEs leading to study drug discontinuation
- Drug-related TEAEs leading to study drug discontinuation

An overall summary table will contain the number and percentage of subjects ever having one of the above listed subsets of AEs. All TEAEs will be summarized for each treatment cohort and overall by MedDRA system organ class (SOC), by SOC and preferred term (PT), and by PT with the number and percentage of subjects. If a subject has more than 1 occurrence of the same TEAE, he/she will be counted only once within that preferred term and system organ class in the summary tables. The most severe occurrence of a repeat TEAE, as well as the closest relationship of the TEAE to the study drug will be used for the analyses.

TEAEs related to study drug, severe TEAEs, SAEs, and TEAEs leading to study drug discontinuation will be summarized in the same manner. That is, summaries will be provided for the numbers and percentages of subjects by SOC, SOC and PT, and PT.

All AEs will be included in by-subject listings. Specific by-subject listings of SAEs and TEAEs leading to study drug discontinuation will be provided. The number of days between first dose and when the event occurred will be presented in listings as well (i.e., relative study day), as will duration of the AE.

3.7.2 Clinical Laboratory Tests

The list of clinical laboratory tests collected during this study is presented in Appendix A of the protocol. Serum chemistry, hematology, and urinalysis results will be summarized with descriptive statistics at Enrollment (based on the last values obtained during TEN-01-301 or TEN-01-302), and Visit 3 (for subjects enrolled from TEN-01-302) or Visit 4 (for subjects enrolled from TEN-01-301) by treatment cohort and overall. For continuous tests, actual values and change from enrollment will be summarized. For categorical tests, the number and percentage of subjects in each category will be presented for each visit. Serum chemistry tests included in these summaries will be 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, and uric acid. Hematology tests included in these summaries will be WBC, RBC, MCV, MCH, MCHC, hemoglobin, hematocrit, and platelet count. Differentials consisting of bands, monophils, neutrophils, eosinophils, lymphocytes, and basophils will be included in the listings only. Urinalysis tests included in these summaries will be appearance, specific gravity, and pH. Protein, glucose, ketones, blood, nitrite, and microscopic results will be presented in listings only.

The frequency of clinically significant abnormal laboratory test values will be tabulated by treatment cohort and overall.

Shift tables classifying normal range results (low out of normal range, normal, or high out of normal range) between enrollment and the final visit will be tabulated by treatment cohort and overall. Missing results for each pairwise summary will be tabulated.

Data listings of clinical laboratory tests will include flags for abnormal results.

3.7.3 Vital Signs and 12-lead Electrocardiogram

Vital signs (body weight, heart rate, respiratory rate, sitting systolic blood pressure, sitting diastolic blood pressure, and temperature) will be summarized descriptively for actual values and change from enrollment values by treatment cohort and overall by visit. Enrollment values for the vital signs will be the last values obtained during TEN-01-301 or TEN-01-302.

Electrocardiogram results (heart rate, PR interval, QRS duration, QT, QTcB and QTcF intervals) will be summarized descriptively for actual values and change from enrollment values by treatment cohort, overall, and visit. Enrollment values will be obtained in a similar manner as for the vital signs. 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.

3.7.4 Physical Examination

Physical examinations (general appearance, HEENT, respiratory, cardiovascular, abdomen, skin, lymph nodes, musculoskeletal, extremities, and neurological) will be summarized at enrollment (last values collected for TEN-01-301 or TEN-01-302), and at Visit 3 or Visit 4. 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.

4. PROGRAMMING SPECIFICATIONS

The programming specifications, including the mock-up validity listings, list of analysis tables, figures, and data listings, will be prepared in a stand-alone document. The programming specification document will be finalized prior to database lock.