Clinical Study Protocol

A 26-Week, Phase 3, Open Label Study with a 12-Week, Placebo-Controlled, Randomized Withdrawal Period Followed by an Open Label Long Term Safety Extension to Evaluate the Safety and Efficacy of Tenapanor to Treat Hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis and Peritoneal Dialysis

Protocol Number: TEN-02-301

30 May 2018

NCT03427125

Clinical Study Protocol

A 26-Week, Phase 3, Open Label Study with a 12-Week, Placebo-Controlled, Randomized Withdrawal Period Followed by an Open Label Long Term Safety Extension to Evaluate the Safety and Efficacy of Tenapanor to Treat Hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis and Peritoneal Dialysis

Protocol Number: TEN-02-301

Edition No. 4:

30 May 2018

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

[redacted]

TABLE OF CONTENTS

TABLE OF CONTENTS 2

IN-TEXT TABLES 5

1 GENERAL INFORMATION 6
1.1 Study Administrative Structure 6
1.2 Synopsis 7
1.3 Schedule of Events 15
1.4 List of Abbreviations 17

2 INTRODUCTION AND BACKGROUND 19
2.1 Introduction 19
2.2 Description of Investigational Product 20
2.3 Description of Active Control 20
2.4 Study Rationale 20
2.5 Risk-Benefit Assessment 21

3 STUDY OBJECTIVES 23
3.1 Primary Objectives 23
3.2 Secondary Objectives 23
3.3 Exploratory Objectives 24

4 STUDY DESIGN 25
4.1 Design Summary 25
4.1.1 Treatments Administered 27
4.1.2 Duration of Study 28

5 SELECTION AND WITHDRAWAL OF PATIENTS 29
5.1 Inclusion Criteria 29
5.2 Exclusion Criteria 30
5.3 Rescreening Criteria 31
5.4 Patient Withdrawal 31
5.5 Early Termination of Study 32
5.6 Restrictions to Patients 32

6 TREATMENT OF PATIENTS 33
6.1 Administration of Investigational Product 33
6.1.1 Identity of Investigational Product(s) 33
6.1.2 Treatments Administered 33
6.1.3 Dose Adjustments 33
6.1.4 Method of Assigning Patients to Treatment Groups 34
6.2 Investigational Product Storage and Accountability 34

6.2.1 Storage Conditions 34
6.2.2 Drug Accountability 34
6.3 Packaging and Labeling 35
6.3.1 Study Drug 35
6.3.2 Blinding Methods 35
6.4 Procedure for Breaking Randomization Code 35
6.4.1 Emergency Unblinding 35
6.5 Prior and Concomitant Therapy 35
6.5.1 Prior Therapy 35
6.5.2 Concomitant Therapy 36

7 COLLECTION OF STUDY VARIABLES 37
7.1 Recording of Data 37
7.2 Data Collection Prior to Enrollment 37
7.3 Safety Variables 37
7.3.1 Physical Examination 38
7.3.2 Vital Signs (blood pressure and heart rate) 38
7.3.3 Electrocardiograms 38
7.3.4 Clinical Laboratory Tests 38
7.3.5 Analysis of Clinical Laboratory Tests 38
7.3.6 Adverse Events 41
7.4 Efficacy Variables 45
7.5 Exploratory Variables 45

8 METHODOLOGY/STUDY VISITS 46
8.1 Screening (Day -21), Visit 1 46
8.2 Wash-out Period (Days -14, -7, and -1), Visits 2, 3 and 4 47
8.3 Randomization (Day 1), Visit 5 47
8.4 Treatment Period (Days 8 and 15 ± 5), Visits 6 and 7 47
8.5 Treatment Period (Days 29 ± 5 and 57 ± 7), Visits 8 and 9 48
8.6 Treatment Period (Day 85 ± 7), Visit 10 48
8.7 Treatment Period (Days 120 and 155 ± 7), Visits 11 and 12 48
8.8 End of 26-week Treatment Period and start of Randomized Withdrawal Period (Day 183 ± 7), Visit 13 49
8.9 Randomized Withdrawal Period (Days 197, 211, 225, 239 and 253 ± 7), Visits 14, 15, 16, 17 and 18 49
8.10 End of Randomized Withdrawal Period and start of Safety Extension Period (Day 267 ± 7), Visit 19 49
8.11 Safety Extension Period (Days 281, 309, 337 ± 7), Visits 20, 21, 22 50
8.12 End of Study (Day 365 ± 7), Visit 23 50
8.13 Unscheduled visits 50
8.14 Withdrawal Procedures 51
8.15 Total Blood Volume Required for Study 51

8.16 Protocol Deviations 51

9 STATISTICAL CONSIDERATIONS 53
9.1 Statistical Analysis Plan 53
9.2 Determination of Sample Size 53
9.3 Analysis Sets 53
9.4 Statistical Methods 54
9.4.1 General Approach 54
9.4.2 Baseline Descriptive Statistics 55
9.4.3 Primary Efficacy Analysis 55
9.4.4 Secondary Efficacy Analyses 55
9.4.5 Procedures for Handling Missing Serum Phosphorus Data 57
9.4.6 Methods of Pooling Data 57
9.4.7 Visit Windows 58
9.4.8 Safety Analyses 58

10 ACCESS TO SOURCE DATA/DOCUMENTS 59

11 QUALITY CONTROL AND QUALITY ASSURANCE 60
11.1 Conduct of Study 60
11.2 Protocol Amendments 60
11.3 Monitoring of Study 60
11.4 ETHICS 61
11.5 Institutional Review Board/Independent Ethics Committee Approval 61
11.5.1 Ethics Review Prior to Study 61
11.5.2 Ethics Review of other Documents 61
11.6 Written Informed Consent 61

12 DATA HANDLING AND RECORD KEEPING 62
12.1 Data Reporting and Case Report Forms 62
12.1.1 Case Report Forms 62
12.1.2 Laboratory Data 62
12.1.3 Retention of Source Documents 62
12.2 Retention of Essential Documents 62

13 ADMINISTRATIVE INFORMATION 63
13.1 Financing and Insurance 63
13.2 Publication Policy 63

14 REFERENCES 64

15 SIGNATURES 65
15.1 Investigator Signature 65
15.2 Sponsor Signature 66

In-Text Tables

Table 7-1 Safety Laboratory Tests 40
Table 8-1 Approximate Blood Volume per Patient 51

1 GENERAL INFORMATION

1.1 Study Administrative Structure

A 26-Week, Phase 3, Open Label Study with a 12-Week, Placebo-Controlled, Randomized Withdrawal Period Followed by an Open Label Long Term Safety Extension to Evaluate the Safety and Efficacy of Tenapanor to Treat Hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis and Peritoneal Dialysis

Sponsor:	Ardelyx, Inc.
Sponsor's Contact:	[redacted]
Medical Monitor:	[redacted]
Study Physician:	[redacted]
Clinical Research Organization:	[redacted]

1.2 Synopsis

Protocol Title: A 26-Week, Phase 3, Open Label Study with a 12-Week, Placebo-Controlled, Randomized Withdrawal Period Followed by an Open Label Long Term Safety Extension to Evaluate the Safety and Efficacy of Tenapanor to Treat Hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis and Peritoneal Dialysis

Sponsor: Ardelyx, Inc.

Study Phase: Phase 3

Objectives: The primary objectives of this study are:

- To evaluate the safety and tolerability of tenapanor for the treatment of hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD) and on Peritoneal Dialysis (ESRD-PD) when administered twice daily for up to 52 weeks.
- To compare the phosphorus lowering effect between tenapanor and placebo based on the change in serum phosphorus (s-P) from the end of the 26-week treatment period to the end of the up to 12-week randomized withdrawal period or the endpoint visit for this period in the responder population (efficacy analysis set).

The secondary objectives of this study are:

- To compare the phosphorus lowering effect between tenapanor and placebo based on the change in serum phosphorus (s-P) from the end of the 26-week treatment period to the end of the randomized withdrawal period or the endpoint visit for this period in the intent-to-treat (ITT) analysis set and at individual doses of tenapanor and placebo in both the efficacy and ITT analysis sets.
- To evaluate the effect of tenapanor on the change in serum phosphorus levels from baseline to the end of 26-week treatment period.
- To evaluate the effect of tenapanor on the number of patients reaching serum phosphorus goal levels defined as < 5.5 mg/dL during the 26-week treatment period.
- To evaluate the effect of tenapanor on Calcium- Phosphorus Product (Ca x P) during all three study periods (26-week treatment period, randomized withdrawal period and safety extension period).
- To evaluate the effect of tenapanor on intact fibroblast growth factor 23 (iFGF23) and c-terminal FGF23 (cFGF23) levels during all three study periods (26-week treatment period, randomized withdrawal period and safety extension period).
- To evaluate the effect of tenapanor on the Kidney Disease Quality of Life (KDQoL) survey during all three study periods.

	• To evaluate the effect of tenapanor on the Dialysis Symptom Index (DSI) survey during all three study periods (for English speakers only). • To compare the long-term safety of tenapanor to the active control sevelamer carbonate. The exploratory objectives of this study are: • To collect and store plasma/serum for future exploratory research into serum/plasma biomarkers related to cardio-renal disease and/or bone-metabolism or that may influence the response (i.e. distribution, safety, tolerability, and efficacy) to tenapanor. (These data will not be part of the study report.)
Number of Sites:	70 to 95 clinical sites in the US
Number of Patients	Approximately 560 ESRD patients on hemo- or peritoneal dialysis.
Study Design and Duration of Treatment:	The study consists of a screening visit, a phosphate binder-free wash-out period of up to four weeks, a 26-week treatment period, an up to 12-week placebo-controlled, randomized withdrawal period, during which patients are randomized 1:1 to remain on the tenapanor dose they are taking at the end of the 26-week treatment or receive placebo, followed by an open label safety extension period for a total treatment period of up to 52 weeks. An active control group, for safety analysis, will receive sevelamer carbonate, open label, for the entire 52-week study period (see Section 2.3). The screening visit (Visit 1) and all other visits in the study must be scheduled after a short dialysis interval (only for HD patients; e.g., Wednesday or Friday for patients on a MWF schedule and Thursday or Saturday for patients on a TThS schedule). Body weight, vital signs and blood collections for laboratory assessments **must** be perfomed pre-dialysis. All other assessments may be perfomed pre-, during, or post-dialysis but should be performed at the same time at each visit. For PD patients, visits should be performed on the same day each week, if possible. Serum phosphorus measured at the screening visit must be ≥4.0 and ≤8.0 mg/dL for patients to be eligible to enter the wash-out period. The wash-out period will begin immediately after the screening visit. Serum phosphorus will be measured weekly (pre-dialysis after a short interval for HD patients) during the wash-out period to determine if the patient meets inclusion criteria for enrollment into the study. The study visits during the wash-out period for HD patients should be scheduled after the first short interval in the week to ensure data are available before a possible randomization, which could then take place after the second short interval in the week. Otherwise the randomization

visit will be scheduled the following week after the first short dialysis interval; therefore, the total length of time off phosphate binder treatment may be up to 4 weeks.

Patients who meet all inclusion/exclusion criteria will be randomized centrally 3:1 to either receive tenapanor at a dose of 30 mg bid or sevelamer carbonate based on package insert instructions (standard of care) after Visits 2, 3 or 4 (after 1, 2, or 3 weeks of wash-out) if they have a s-P level of at least 6.0 mg/dL and not more than 10.0 mg/dL and have an increase in s-P of at least 1.5 mg/dL versus pre wash-out (Visit 1, Screening Visit).

Patients randomized into the tenapanor group will receive tenapanor at a dose of 30 mg bid. Tenapanor will be taken twice daily; just prior to breakfast and dinner. Patients on HD should **not** take tenapanor at the meal immediately preceding dialysis; in this case, patients will take tenapanor prior to the next meal after dialysis. Those randomized into the active control group will take sevelamer carbonate based on standard of care using the package insert for guidance for the entire 52-week study period. Patients who are on active control will **not** have Visits 14, 16 and 18.

Investigators may decrease or increase the dose of tenapanor based on s-P levels and/or GI tolerability in 10 mg increments to a minimum of 10 mg bid or a maximum of 30 mg bid from enrollment until Day 183 (Visit 13). The dose of sevelamer carbonate may be adjusted based on standard of care for the entire 52-week study period.

During the 26-week treatment period and the safety extension period, patients on tenapanor with a s-P $\geq$ 10 mg/dL at any time after Week 2 of treatment or patients with a s-P $\geq$ 9 mg/dL for two consecutive visits after Week 2 will be discontinued and all visit procedures for Visit 23 will be completed, if possible. Patients in the active control group, receiving sevelamer carbonate do not have specific discontinuation criteria; they will be treated based on standard of care using the package insert for guidance.

At the end of the 26-week treatment period, patients in the tenapanor group only will be randomized 1:1 to either remain on the tenapanor dose they are taking on Day 183 (Visit 13) or receive placebo for up to an additional 12 weeks (randomized withdrawal period). During the randomized withdrawal period, patients with a s-P $\geq$ 9 mg/dL will be discontinued and all visit procedures for Visit 23 will be completed, if possible. Patients who discontinue from the randomized withdrawal period with s-P $\geq$ 9 mg/dL will be offered the opportunity to enter the safety extension period. In addition, patients who randomize into the

tenapanor group and complete the randomized withdrawal period are eligible to enroll in the open label safety extension period for an additional 14 weeks. Patients who enroll into the open label extension period will receive tenapanor.

Laboratory efficacy endpoints will be assessed at designated visits throughout the study; s-P will be measured at every visit.

Safety assessments will be performed during the study and will include physical examinations, vital signs (blood pressure and pulse), body weights, clinical laboratory evaluations, 12-lead electrocardiograms (ECGs), and adverse event (AE) monitoring

Planned Sample Size:

Approximately 560 male and female patients with end stage renal disease (ESRD) on chronic maintenance hemodialysis (HD) 3 times a week for a minimum of 3 months or chronic maintenance peritoneal dialysis (PD) for a minimum of 6 months are eligible to participate. Patients will be randomized 3:1 to receive either tenapanor or active control.

Patient Selection Criteria:

Inclusion criteria:

1. Signed and dated informed consent prior to any study specific procedures.
2. Males or females $\geq$ 18 years of age.
3. Females must be non-pregnant, non-lactating and fulfilling one of the following:
   a. Post–menopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle stimulating hormone (FSH) levels in the laboratory defined post-menopausal range.
   b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
   c. Use of acceptable contraceptive method: IUD with spermicide, a female condom with spermicide, contraceptive sponge with spermicide, an intravaginal system (e.g., NuvaRing®), a diaphragm with spermicide, a cervical cap with spermicide, or oral, implantable, transdermal, or injectable contraceptives, sexual abstinence, or a sterile sexual partner.
4. Males must agree to avoid fathering a child (or donating sperm), and therefore be either sterile (documented) or agree to use, from the time of enrollment until 45 days after end of study, one of the following approved methods of contraception: a male condom with

spermicide, a sterile sexual partner, use of an IUD with spermicide by female sexual partner, a female condom with spermicide, contraceptive sponge with spermicide, an intravaginal system (e.g., NuvaRing®), a diaphragm with spermicide, a cervical cap with spermicide, or oral, implantable, transdermal, or injectable contraceptives.

5. Chronic maintenance hemodialysis 3x/week for at least 3 months or chronic maintenance peritoneal dialysis (PD) for a minimum of 6 months. If modality of dialysis has changed, patient must meet one of the two dialysis criteria above and been on the new modality of dialysis for a minimum of one month.
6. Stable vascular access as assessed by Investigator, if on HD.
7. Kt/V ≥1.2 at most recent measurement prior to screening.
8. Prescribed and taking at least 3 doses of phosphate binder per day. The prescribed dose should have been unchanged during the last 3 weeks prior to screening.
9. Serum phosphorus levels must be between 4.0 and 8.0 mg/dL (inclusive) at screening, analyzed at the central laboratory used in the study.
10. Intentionally left blank.
11. For enrollment in the study, patients must have serum phosphorus levels of at least 6.0 mg/dL but not more than 10.0 mg/dL and have had an increase of at least 1.5 mg/dL versus pre wash-out value after 1, 2 or 3 weeks wash-out of phosphate binders.
12. Able to understand and comply with the protocol.

Exclusion criteria:

1. Severe hyperphosphatemia defined as serum phosphorus greater than 10.0 mg/dL on phosphate-binders at any time point during clinical monitoring for the 3 preceding months before the screening visit.
2. Serum/plasma parathyroid hormone >1200 pg/mL. The most recent value from patients' medical records should be used.
3. Clinical signs of hypovolemia at enrollment as judged by the investigator.
4. History of inflammatory bowel disease (IBD) or diarrhea predominant irritable bowel syndrome (IBS-D).
5. Scheduled for living donor kidney transplant, plans to change to a different method of dialysis, home HD or plans to relocate to another center during the study period.

6. Any evidence of or treatment of malignancy within one year, excluding non- melanomatous malignancies of the skin.
7. Positive serology (hepatitis C or B infection, or human immunodeficiency virus) **with** evidence of significant hepatic impairment or WBC elevation according to the Investigator.
8. History of alcohol abuse, illicit drug use, significant mental illness, or any history of drug abuse or addiction within 12 months of study enrollment.
9. Life expectancy <12 months.
10. Use of an investigational agent within 30 days prior to Screening.
11. Previous randomization into this study.
12. Previous exposure to tenapanor.
13. Involvement in the planning and/or conduct of the study (applies to both Ardelyx/CRO staff and/or staff at the study site).
14. If, in the opinion of the Investigator, the patient is unable or unwilling to fulfill the requirements of the protocol or has a condition which would render the results uninterpretable.

Study Drug: Tenapanor 10 mg tablets and matched placebo

Active Control: Sevelamer carbonate tablets (800 mg)

Dose and Route of Administration: Tenapanor will be administered PO at the following dose levels:

- 26-week treatment period: Titration scheme (from Randomization (Visit 5) to Day 183 (Visit 13): starting dose 30 mg bid, dosing may be down-titrated or up-titrated to a maximum of 30 mg bid in a step-wise fashion based on serum phosphorus levels and/or GI tolerability. Down-titration can go from 30 mg bid to 20 mg bid to 10 mg bid. Dose escalation can go in 10 mg bid increments to a maximum dose of 30 mg bid.
- Randomized withdrawal period: Fixed dose based on last dose from 26-week treatment period.
- Safety extension period: Starting dose is the same dose from the end of the 26-week treatment period. Titration is allowed as described for the 26-week treatment period.

Sevelamer carbonate (active control) will be administered PO based on standard of care during the entire 52-week study period.

Placebo will be administered PO during the randomized withdrawal period only. During this period, patients will be randomized 1:1 to receive either placebo or tenapanor. The placebo group will receive the

same number of tablets as the last dose of tenapanor they received during the 26-week treatment period. Patients from the active control group will not enter the randomized withdrawal period; they will continue to receive sevelamer carbonate per standard of care for all 52 weeks.

A detailed description of the dose adjustment procedures can be found in Section 6.1.3.

Statistical Analyses:

Analysis sets:

Safety Analysis Set (at each study period):

All patients who receive at least one dose of study drug (tenapanor or placebo) or active control for the individual study period. The safety analysis set will be used for the analysis of all safety variables.

Intent to Treat (ITT) Analysis Set (at each study period):

All patients who meet the study entry inclusion/exclusion criteria, receive at least one dose of tenapanor or placebo, and have at least one post-treatment serum phosphorus for the individual study period. The ITT analysis set will be used for the analysis of all efficacy variables.

Efficacy Analysis Set (12-week randomized withdrawal period):

All patients who meet the study entry inclusion and exclusion criteria, receive at least one dose of tenapanor during the 26-week treatment period, complete the 26-week treatment period, and achieve at least a 1.2 mg/dL reduction in serum phosphorus from baseline to the end of the 26-week treatment. The efficacy analysis set will be used for the primary efficacy analysis.

Per-Protocol (PP) Analysis Set (12-week randomized withdrawal period):

All patients in the ITT analysis set who completed the 12-week randomized withdrawal period as planned with no major protocol deviations that impact the primary efficacy variable. The PP analysis set will be used for sensitivity analyses to support the primary and key secondary efficacy analyses.

Efficacy analyses:

All efficacy variables will be summarized by treatment (including dose, if applicable) group, using descriptive statistics. All continuous efficacy variables (s-P, Ca x P, iFGF23, cFGF23, KDQoL and DSI) will be analyzed using an analysis of covariance (ANCOVA) model with terms for pooled investigator site, treatment (including dose, if

applicable), and baseline as the covariable. The change from baseline will be the dependent variable. The least squares means (LSmeans) will be presented for the change from baseline values for each treatment group (including dose, if applicable) with the 95% confidence interval (CI).

The primary efficacy variable will be the change in serum phosphorus from the end of the 26-week treatment period to the end of the 12-week randomized withdrawal period or the endpoint visit for this period. The primary efficacy analysis will be based on the difference between the tenapanor treatment and placebo treatment group in the responder population (efficacy analysis set). Endpoint for this analysis is defined as the last serum phosphorus lab value assessment during and up to the end of the 12-week randomized withdrawal period.

Secondary analyses are described in Section 9 and are detailed in the statistical analysis plan (SAP).

Safety analyses:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class, preferred term, and treatment (including dose, if applicable) group. For a change in stool form and/or frequency to be considered an adverse event, the criteria detailed in Section 7.3.6.1 must be followed. These summaries will be provided for each study period separately.

Actual values and change from baseline values for clinical laboratory tests, vital signs, body weights, and ECGs will be summarized by each treatment (including dose, if applicable) group for each visit collected during the study. The number and percentage of patients in each physical examination category will be presented for each visit by treatment (including dose, if applicable) group. These summaries will be provided for each study period separately.

1.3 Schedule of Events

	Screening	Washout[h]			26-Week Treatment Period								
Study Day	-21	-14 ±2	-7 ±2	-1 ±2	1	8 ±5	15 ±5	29 ±5	57 ±7	85 ±7	120 ±7	155 ±7	183 ±7
Visit	V1	V2	V3	V4[n]	V5[n]	V6	V7	V8	V9	V10	V11	V12	V13
Informed consent	X												
Inclusion/Exclusion	X	X	X	X	X								
Demographics	X												
Pre-dialysis Body Weight	X[f]				X					X			X
Kt/V[e]	X												
KDQoL/DSI[j]	X									X			X
Med/Surgical Hx	X	X	X	X	X								
Physical Exam	X				X								X
Vital signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG evaluation	X				X					X			X
Clinical laboratory tests[b]	X				X					X			X
FSH test[c]	X												
Pregnancy test[c] (serum)	X				X					X			X
HIV, hepatitis B and C tests	X												
Start wash-out of phosphate binders	X												
Randomization #1[k]					X								
Drug dispense					X	X		X	X	X	X	X	
Drug return						X		X	X	X	X	X	X
Drug accountability[l]						X		X	X	X	X	X	X
s-Phosphorus[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Ca x P, FGF23	X				X					X			X
Exploratory biomarkers	X				X					X			X
AE assessment[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/ConMeds	X	X	X	X	X	X	X	X	X	X	X	X	X

	Randomized Withdrawal Period[g]							Safety Extension Period			
Study Day	183 +7	197 +7	211 +7	225 +7	239 +7	253 +7	267 +7	281 +7	309 +7	337 +7	365 +7
Visit	V13	V14[m]	V15	V16[m]	V17	V18[m]	V19	V20	V21	V22	V23/ EOT
Pre-dialysis Body Weight							X			X	X
KDQoL/DSI[j]							X				X
Physical Exam							X				X
Vital signs[a]		X	X	X	X	X	X	X	X	X	X
ECG evaluation							X				X
Clinical laboratory tests[b]							X				X
Pregnancy test[c] (serum)							X				X
Randomization #2[k]	X										
Drug dispense	X	X	X	X	X	X	X	X	X	X	
Drug return		X	X	X	X	X	X	X	X	X	X
Drug accountability		X	X	X	X	X	X	X	X	X	X
s-Phosphorus[i]		X	X	X	X	X	X	X	X	X	X
Ca x P, FGF23			X		X		X				X
Exploratory biomarkers			X		X		X				X
AE assessment[d]	X	X	X	X	X	X	X	X	X	X	X
Prior/ConMeds	X	X	X	X	X	X	X	X	X	X	X

a Vital signs include blood pressure, pulse and must be performed pre-dialysis.
b All blood collections are performed pre-dialysis.
c FSH test and pregnancy test are performed on all females at Screening. After screening, pregnancy tests will only be performed on females of child-bearing potential.
d AEs and SAEs will be collected from consenting to the end of study.
e Kt/V should be the most recent historical value prior to screening.
f Height will also be measured at the screening visit
g In the randomized withdrawal period, patients in the tenapanor group only are randomized 1:1 to either stay on current treatment of tenapanor or receive a matched placebo; based on withdrawal criteria, patients may enter the safety assessment period at any visit.
h If the laboratory evaluations from the wash-out period deem the patient ineligible for the study, the site must inform the patient and tell them to take their phosphate binders.
i s-Phosphorus sample collected at visits when safety labs are not collected.
j KDQoL (KDQoL™-36), Kidney Disease and Quality of Life survey. DSI, Dialysis Symptom Index survey is for English speakers only and is not validated in other languages.
k Randomization #1 is 3:1, tenapanor: active control. Randomization #2 is 1:1 from the tenapanor group only to tenapanor: placebo. Patients in the active control group will receive sevelamer carbonate for the entire 52-week study period.
l Drug accountability will be performed for both tenapanor and the active control.
m Visits 14, 16 and 18 are not done for subjects randomized into the active control group.
n Patients should be randomized by the week after meeting s-P washout criteria;total period off binder must not be greater than 4 weeks.

1.4 List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransaminase
ANOVA	Analysis of variance
AST	Aspartate aminotransaminase
BID	bis in die, twice per day
BMI	Body mass index
CKD	Chronic kidney disease
eCRF	Electronic case report form
CSR	Clinical study report
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ESRD	End-stage renal disease
ESRD-PD	End-stage renal disease on peritoneal dialysis
FDA	US Food and Drug Administration
iFGF23	Intact Fibroblast growth factor 23
cFGF23	c-terminus Fibroblast growth factor 23
FSH	Follicle-stimulating hormone level
GCP	Good Clinical Practice
GI	Gastrointestinal
H+	Hydrogen
HD	Hemodialysis
HF	Heart Failure
HIV	Human Immunodeficiency Virus
IB	Investigational Brochure
IBS	Irritable bowel syndrome
IBS-C	Constipation-predominant irritable bowel syndrome
IBS-D	Diarrhea-predominant irritable bowel syndrome
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board

IUD	Intrauterine device
LOCF	Last observation carried forward
LOQ	Limit of quantitation
LSmean	Least squares mean
MAD	Multiple ascending-dose
min	Minimum (e.g., min, max)
n,	Number of observed patients
N	Number of patients in the applicable analysis set
Na+	Sodium
NHE3	Na/hydrogen antiporter 3
NOAEL	No observed adverse effect level
p	Probability; p-value
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Oral administration
PTH	Parathyroid hormone
QD	quaque die, once per day
QRS	Principal deflection in ECG
QT	ECG interval
QT_c	QT interval which has been corrected by taking into account heart rate
RAASi	Renin–angiotensin–aldosterone system inhibitors
RBC	Red blood cell
s-	serum
SAD	Single ascending-dose
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TEER	Transepithelial electronic resistance
TID	ter in die, three times per day
WBC	White blood cell

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

Chronic kidney disease (CKD) affects 5-10% of the population globally and the numbers of patients suffering from end-stage renal disease (ESRD) are increasing (Eknoyan 2004). With progressing impairment of renal function, the ability of the kidneys to appropriately excrete phosphate is reduced and hyperphosphatemia is a nearly universal complication of ESRD. Hyperphosphatemia is also part of the CKD Bone Mineral Disorder, which is associated with a disruption of normal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones such as parathyroid hormone (PTH) and vitamin D. Left untreated, hyperphosphatemia can lead to vascular and tissue calcifications, bone pain, fractures and worsening secondary hyperparathyroidism and is associated with increased cardiovascular morbidity and mortality. Observational data show that treatment with phosphate binders to reduce hyperphosphatemia is independently associated with improved survival (Waheed 2013), and a meta-analysis of randomized clinical trials demonstrate that non-calcium based binders have a lower mortality as compared to calcium-based binders (Jamal et al in the Lancet, published online July 19, 2013). Experimental studies provide support for the epidemiologic findings: phosphate excess promotes vascular calcification, induces endothelial dysfunction and may contribute to other emerging chronic kidney disease-specific mechanisms of cardiovascular toxicity (Waheed 2013). Hence, clinical treatment guidelines for patients with advanced kidney disease suggest maintaining serum phosphorus within 3.5 to 5.5 mg/dL, which is close to the normal range (KDIGO guideline 2009).

In addition to dietary phosphorus restrictions and dialysis, 80-90% of ESRD patients need treatment with oral phosphate binders. However, a significant proportion of ESRD patients still don't achieve adequate phosphate control (DOPPS Annual Report 2010). An important barrier for a successful treatment is the pill burden associated with all phosphate binders, which have to be dosed in several grams per day and taken with each meal to bind dietary phosphorus. The side effect profile with poor gastro-intestinal tolerability and concerns for long-term negative effects such as tissue calcification and potential metal accumulation toxicity from calcium-based and metal-based binders, respectively, further impair an effective phosphorus control in ESRD patients. There is, therefore, a rationale to develop oral phosphate-lowering drugs with new mechanisms of action, a more convenient dosing and improved risk-benefit profile.

Tenapanor is an oral, minimally absorbed compound that inhibits the NHE3 (sodium hydrogen exchanger) transporter locally in the gastrointestinal tract, which leads to reduced sodium (and fluid) absorption. Data from pre-clinical studies and results in healthy volunteers show that tenapanor also reduces the uptake of phosphorus from the gut.

Tenapanor reduces intestinal phosphate absorption, predominantly through reduction of passive paracellular phosphate influx, the most important overall mechanism of intestinal phosphate absorption. Tenapanor modulates tight junctions to increase TEER, thereby reducing paracellular phosphate permeability; this effect is mediated exclusively via on-target NHE3 inhibition.

Tenapanor has been administered to approximately 347 healthy subjects at single doses up to 900 mg, and in repeated doses up to 180 mg/day for 7 days, and to approximately 1020 IBS-C patients at doses up to 100 mg/day for up to 12 weeks and to 477 CKD patients (CKD stages 3b, 4 and 5D) for up to 12 weeks at doses up to 120 mg/day.

2.2 Description of Investigational Product

Tenapanor is a GI-acting, minimally systemic, NHE3 inhibitor. Tenapanor is administered as the hydrochloride salt and 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 $C_{50}H_{68}Cl_6N_8O_{10}S_2$.

[redacted]

Dosing consists of one to three 10 mg tablets, taken in conjunction with breakfast and dinner.

[redacted] Tablets of tenapanor should be stored in the original packaging according to the labeling.

2.3 Description of Active Control

The active control used in this study will be sevelamer carbonate and will be supplied as commercially available (270 tablet count bottles) by the sponsor. Sevelamer carbonate must be stored in the original packaging as described on the label.

The dose prescribed will be based on standard of care using the package insert for guidance.

2.4 Study Rationale

Reduction of phosphorus uptake is an established treatment approach for hyperphosphatemia in ESRD-HD patients and a number of drugs that bind dietary phosphorus in the gut lumen are part of the standard of care for patients with advanced kidney disease on dialysis. Results from both Phase 2b and Phase 3 studies in ESRD-HD patients with hyperphosphatemia, showed that tenapanor produced a statistically significant decrease in serum phosphorus; these results suggest

that tenapanor has the potential to provide phosphorus control comparable to existing phosphate-lowering agents and improved dosing with reduced pill burden, which merits further clinical development.

2.5 Risk-Benefit Assessment

This risk-benefit assessment is based on the nonclinical toxicology, safety, and pharmacology studies as well as the 19 clinical trials performed with tenapanor; the results from this research are described in the Investigator's Brochure.

Pre-clinical toxicological studies up to 9 months have been performed in rodents and dogs. The toxicological profile includes soft stools and/or diarrhea and findings secondary to dehydration; these findings are an expected manifestation of the compound's exaggerated pharmacologic activity and findings were reversible during the recovery period without drug. A two-year carcinogenicity study in Sprague-Dawley rats was negative.

The safety, tolerability, pharmacodynamics and efficacy of tenapanor have been evaluated in 347 healthy subjects at single doses up to 900 mg, and in repeated doses up to 180 mg/day for 7 days, and to 1020 IBS-C patients at doses up to 100 mg/day for up to 12 weeks and to 477 CKD patients (CKD stages 3b, 4 and 5D) for up to 12 weeks at doses up to 120 mg/day.

Tenapanor has minimal systemic bioavailability. Less than 1% of plasma pharmacokinetics samples collected during human studies (>3000) have quantifiable tenapanor present in blood serum (lower limit of quantification = 0.5 ng/mL); all samples with tenapanor were below 1.5 ng/mL.

The reduction in sodium uptake results in an increase in net fluid volume in the intestinal tract. Based on this mechanism of action, tenapanor has the potential to produce softer/looser stools and increased stool frequency. Tenapanor has been generally safe and well tolerated in clinical studies and the safety profile with softening/loosening of stool consistency and gastro-intestinal adverse events have been consistent with its pharmacology.

The theoretical adverse effects from tenapanor treatment in ESRD patients would be due to exaggerated pharmacological effects and may include electrolyte disturbances, metabolic acidosis, soft stools/diarrhea and reduced blood pressure. While a softening/loosening of the stool with an increased fluid loss via the intestine is an intended and desired effect of tenapanor in some patients, sensitive patients should be monitored for signs of dehydration in case of prolonged severe diarrhea. This study protocol includes clinical laboratory tests (including bicarbonate and electrolytes) and vital signs as well as specific discontinuation criteria related to phosphate control to mitigate risks to study participants as well as to reduce the risk for severe hyper- or hypophosphatemia during the study and limit the period with risk for suboptimal phosphate control. All patients will re-start their pre-study treatment with phosphate binders when their participation in the study ends. ESRD-HD patients are dialyzed three times per week

and their health status is checked at each visit as part of standard of care. See the Investigators Brochure for details on non-clinical and clinical results with tenapanor.

Patients will be informed both verbally and in writing about these aspects before taking part in any study-specific examination and the study will be conducted under conditions that ensure a high probability for the early detection of untoward events and for appropriate intervention.

In summary, the risks to the participants in this up to one year study are considered acceptable and the study results will be important for the development of a potential new drug, which could improve the treatment of hyperphosphatemia in this patient group.

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the safety and tolerability of tenapanor for the treatment of hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD) and on Peritoneal Dialysis (ESRD-PD) when administered twice daily for up to 52 weeks.
- To compare the phosphorus lowering effect between tenapanor and placebo based on the change in serum phosphorus (s-P) from the end of the 26-week treatment period to the end of the up to 12-week randomized withdrawal period or the endpoint visit for this period in the responder population (efficacy analysis set).

3.2 Secondary Objectives

The secondary objectives of this study are:

- To compare the phosphorus lowering effect between tenapanor and placebo based on the change in serum phosphorus (s-P) from the end of the 26-week treatment period to the end of the randomized withdrawal period or the endpoint visit for this period in the intent-to-treat (ITT) analysis set and at individual doses of tenapanor and placebo in both the efficacy and ITT analysis sets.
- To evaluate the effect of tenapanor on the change in serum phosphorus levels from baseline to the end of 26-week treatment period
- To evaluate the effect of tenapanor on the number of patients reaching serum phosphorus goal levels defined as < 5.5 mg/dl during the 26-week treatment period.
- To evaluate the effect of tenapanor on Calcium- Phosphorus Product (Ca x P) during all three study periods (26-week treatment period, randomized withdrawal period and safety extension period).
- To evaluate the effect of tenapanor on intact fibroblast growth factor 23 (iFGF23) and c-terminal FGF23 (cFGF23) levels during all three study periods (26-week treatment period, randomized withdrawal period and safety extension period).
- To evaluate the effect of tenapanor on the Kidney Disease Quality of Life (KDQoL) survey during all three study periods.
- To evaluate the effect of tenapanor on the Dialysis Symptom Index (DSI) survey during all three study periods (for English speakers only).
- To compare the long-term safety of tenapanor to the active control sevelamer carbonate.

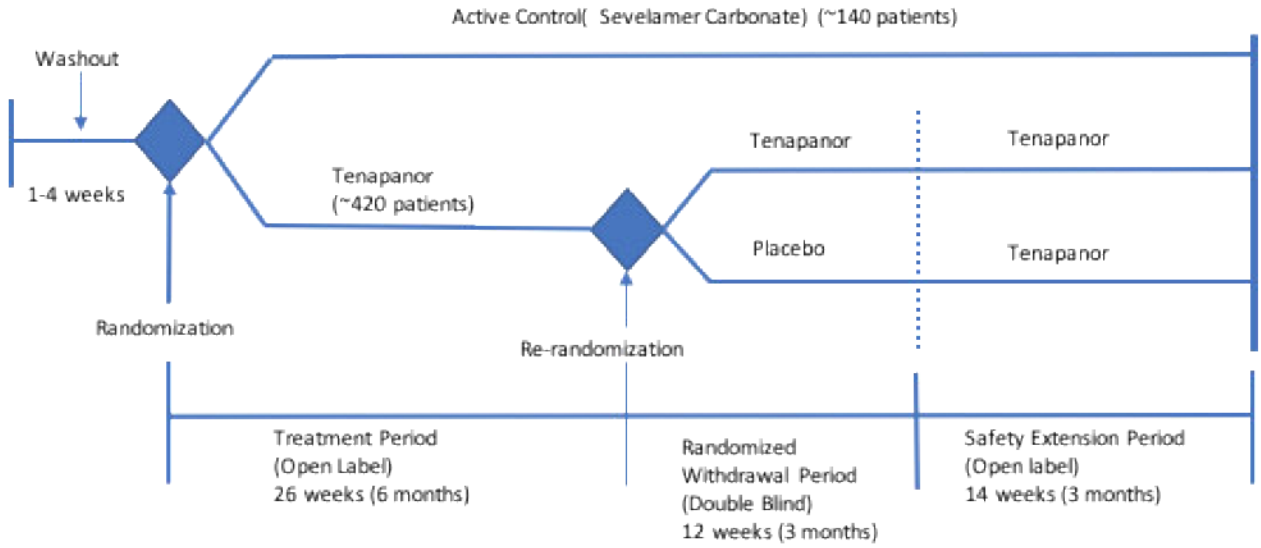
3.3 Exploratory Objectives

The exploratory objectives of this study are:

- To collect and store plasma/serum for future exploratory research into serum/plasma biomarkers related to cardio-renal disease and/or bone-metabolism or that may influence the response (i.e. distribution, safety, tolerability, and efficacy) to tenapanor. These data will not be part of this study report.

4 STUDY DESIGN

4.1 Design Summary



The study consists of a screening visit, a phosphate binder-free wash-out period of up to four weeks, a 26-week treatment period, an up to 12-week placebo-controlled, randomized withdrawal period during which patients are randomized 1:1 to either remain on the tenapanor dose they are taking at the end of the 26-week treatment period or receive placebo, followed by an open label safety extension period for a total treatment period of up to 52 weeks. An active control group, for safety analysis, will receive sevelamer carbonate, open label, for the entire 52-week study period (see Section 2.3).

The screening visit (Visit 1) and all other visits in the study must be scheduled after a short dialysis interval (only for HD patients; e.g., Wednesday or Friday for patients on a MWF schedule and Thursday or Saturday for patients on a TThS schedule). Body weight, vital signs and blood collections for laboratory assessments **must** be perfomed pre-dialysis. All other assessments may be perfomed pre-, during, or post-dialysis but should be performed at the same time at each visit. For PD patients, visits should be performed on the same day each week, if possible. For all patients, serum phosphorus measured at the screening visit must be ≥4.0 and ≤8.0 mg/dL or patients to be eligible to enter the wash-out period.

The wash-out period will begin immediately after the screening visit. Serum phosphorus will be measured weekly (pre-dialysis after a short interval for HD patients) during the wash-out period to determine if the patient meets inclusion criteria for enrollment into the study.

The study visits during the wash-out period for HD patients should be scheduled after the first short interval in the week to ensure data is available before a possible randomization, which could then take place after the second short interval in the week. Otherwise the randomization visit will be scheduled the following week after the first short dialysis interval; therefore, the total length of phosphate binder wash-out may be up to 4 weeks.

The wash out period will be a minimum of 1 week and must not exceed 4 weeks. Patients should be randomized by one week after meeting s-P washout criteria (after visit 2, 3 or 4); the total washout period must not be greater than 4 weeks.

Patients who meet all the inclusion/exclusion criteria will be randomized 3:1 to either receive tenapanor at a dose of 30 mg bid or sevelamer carbonate based on package insert instructions (standard of care) after Visits 2, 3 or 4 (after 1, 2 or 3 weeks of wash-out) if they have a s-P level of at least 6.0 mg/dL and not more than 10.0 mg/dL and have an increase in s-P of at least 1.5 mg/dL versus pre wash-out (Visit 1, Screening visit).

Patients randomized into the tenapanor group will receive tenapanor at a dose of 30 mg bid. Tenapanor will be taken twice daily; just prior to breakfast and dinner. Patients on HD should **not** take tenapanor at the meal immediately preceding dialysis; in this case, patients will take tenapanor prior to the next meal after dialysis. Those randomized into the active control group will take sevelamer carbonate based on standard of care using the package insert for guidance for the entire 52-week study period. Patients who are on active control will **not** have Visits 14, 16 and 18.

Investigators may decrease or increase the dose of tenapanor based on s-P levels and/or GI tolerability. The changes must be made in 10 mg increments to a minimum of 10 mg bid or a maximum of 30 mg bid from enrollment until Day 183 (Visit 13). The dose of sevelamer carbonate may be adjusted based on standard of care for the entire 52-week study period.

During the 26-week treatment period and the safety extension period, patients on tenapanor with a s-P $\geq$ 10 mg/dL at any time after Week 2 of treatment or patients with a s-P $\geq$ 9 mg/dL for two consecutive visits after Week 2 will be discontinued and all visit procedures for Visit 23 will be completed, if possible. Patients in the active control group, receiving sevelamer carbonate do not have specific discontinuation criteria; they will be treated based on standard of care using the package insert for guidance.

At the end of the 26-week treatment period, patients in the tenapanor group only will be randomized 1:1 to either remain on the tenapanor dose they are taking on Day 183 (Visit 13) or receive placebo for up to an additional 12 weeks (randomized withdrawal period). During the randomized withdrawal period, patients with a s-P $\geq$ 9 mg/dL will be discontinued and all visit procedures for Visit 23 will be completed, if possible. Patients who discontinue from the

randomized withdrawal period with s-P ≥ 9 mg/dL will be offered the opportunity to enter the safety extension period.

Patients who randomize into the tenapanor group and complete the randomized withdrawal period are eligible to enroll in the open label safety extension period for an additional 14 weeks. Patients who enroll in the open label safety period will receive tenapanor during this period.

Laboratory efficacy endpoints will be assessed at various times throughout the study; s-P will be measured at every visit.

Safety assessments will be performed during the study and will include physical examination, vital signs (BP/P), body weights, clinical laboratory evaluations, 12-lead electrocardiograms (ECGs), and adverse event (AE) monitoring. Blood samples will be collected and stored, as appropriate, for the potential evaluation of exploratory biomarkers related to cardio-renal disease or bone metabolism or that may influence the response (i.e. distribution, safety, tolerability, and efficacy) to tenapanor.

Details of study assessments and the schedule of events for this study are in Section 1.3.

4.1.1 Treatments Administered

At randomization (Visit 5), patients will be randomized to either tenapanor or the active control group. Patients randomized into the active control group will receive sevelemer carbonate for the entire 52-week study period. Dose of sevelamer will be adjusted per standard of care using the package insert for guidance.

Patients randomized into the tenapanor group will receive tenapanor at a dose of 30 mg bid. Tenapanor will be taken twice daily; just prior to breakfast and dinner. Tenapanor is supplied as 10 mg tablets; each dose of one to three tablets bid will achieve total daily doses of 20, 40, or 60 mg tenapanor.

The dose of tenapanor may be down titrated or up titrated to a max of 30 mg bid in a step-wise fashion based on serum-phosphorus levels and/or GI tolerability (detailed in Section 6.1.3). Down-titration can go from 30 mg bid to 20 mg bid and 20 mg bid to 10 mg bid. Dose escalation can go in 10 mg bid increments to a maximum dose of 30 mg bid.

On dialysis days, patients on HD should **not** take study drug at the meal prior to dialysis and instead take it before another meal. If a meal is skipped, the dose should be taken with another meal during the day or at around the time that the meal would have been consumed. Active control (sevelamer carbonate) will be taken based on standard of care using the package insert for guidance.

During the randomized withdrawal period, patients in the tenapanor group only will be randomized to either remain on their current dose of tenapanor or receive placebo in a 1:1 ratio.

Placebo will be administered PO during the randomized withdrawal period only for patients randomized into placebo from the tenapanor group. The same number of tablets as the last dose of tenapanor during 26-week treatment period will be administered to the placebo group. Patients from the active control group will not enter the randomized withdrawal period; they will continue to receive sevelamer carbonate per standard of care for the entire 52-week study period.

During the safety extension period, patients on tenapanor will continue at their same dose. Patients on placebo will continue with their same dose from the end of the 26-week treatment period. Titration is allowed as described for the 26-week treatment period.

4.1.2 Duration of Study

The expected duration of each patient's participation in the study will be up to 56 weeks. The screening period can be up to 4 weeks and the total of all three treatment periods can be up to 52 weeks.

5 SELECTION AND WITHDRAWAL OF PATIENTS

Investigator(s) will record in the patient screening log all patients who sign the informed consent form for entry into the study.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study.

5.1 Inclusion Criteria

A patient will be eligible for study participation if he/she meets the following criteria:

1. Signed and dated informed consent prior to any study specific procedures.
2. Males or females ≥ 18 years of age.
3. Females must be non-pregnant, non-lactating and fulfilling one of the following:
    a. Post –menopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle stimulating hormone (FSH) levels in the laboratory defined post-menopausal range.
    b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation.
    c. Use of acceptable contraceptive method: IUD with spermicide, a female condom with spermicide, contraceptive sponge with spermicide, an intravaginal system (e.g., NuvaRing®), a diaphragm with spermicide, a cervical cap with spermicide, or oral, implantable, transdermal, or injectable contraceptives, sexual abstinence, or a sterile sexual partner.
4. Males must agree to avoid fathering a child (or donating sperm), and therefore be either sterile (documented) or agree to use, from the time of enrollment until 45 days after end of study, one of the following approved methods of contraception: a male condom with spermicide, a sterile sexual partner, use of an IUD with spermicide by female sexual partner, a female condom with spermicide, contraceptive sponge with spermicide, an intravaginal system (e.g., NuvaRing®), a diaphragm with spermicide, a cervical cap with spermicide, or oral, implantable, transdermal, or injectable contraceptives.
5. Chronic maintenance hemodialysis 3x/week for at least 3 months or chronic maintenance peritoneal dialysis (PD) for a minimum of 6 months. If modality of dialysis has changed patient must meet one of the two dialysis criteria above and been on the new modality of dialysis for a minimum of one month.
6. Stable vascular access as assessed by Investigator if on HD.
7. Kt/V ≥1.2 at most recent measurement prior to screening.
8. Prescribed and taking at least 3 doses of phosphate binder per day. The prescribed dose should have been unchanged during the last 3 weeks prior to screening.

9. Serum phosphorus levels should be between 4.0 and 8.0 mg/dL (inclusive) at screening analyzed at the central laboratory used in the study.
10. Intentionally left blank.
11. For enrollment in the study, patients must have serum phosphorus levels of at least 6.0 mg/dL but not more than 10.0 mg/dL and have had an increase of at least 1.5 mg/dL versus pre wash-out value after 1, 2 or 3 weeks wash-out of phosphate binders.
12. Able to understand and comply with the protocol.

5.2 Exclusion Criteria

A patient will not be eligible for study participation if he/she meets any of the exclusion criteria, or will be discontinued at the discretion of the Investigator if he/she develops any of the following exclusion criteria during the study:

1. Severe hyperphosphatemia defined as serum phosphorus greater than 10.0 mg/dL on Phosphate-binders at any time point during clinical monitoring for the 3 preceding months before the screening visit.
2. Serum/plasma parathyroid hormone >1200 pg/mL. The most recent value from patients' medical records should be used.
3. Clinical signs of hypovolemia at enrollment as judged by the Investigator.
4. History of inflammatory bowel disease (IBD) or diarrhea predominant irritable bowel syndrome (IBS-D).
5. Scheduled for living donor kidney transplant, plans to change to a different method of dialysis, home HD or plans to relocate to another center during the study period.
6. Any evidence of or treatment of malignancy within one year, excluding non- melanomatous malignancies of the skin.
7. Positive serology (hepatitis C or B infection, or human immunodeficiency virus) **with** evidence of significant hepatic impairment or WBC elevation according to the Investigator.
8. History of alcohol abuse, illicit drug use, significant mental illness, or any history of drug abuse or addiction within 12 months of study enrollment.
9. Life expectancy < 12 months.
10. Use of an investigational agent within 30 days prior to Screening.
11. Previous randomization into this study.
12. Previous exposure to tenapanor
13. Involvement in the planning and/or conduct of the study (applies to both Ardelyx/CRO staff and/or staff at the study site).

14. If, in the opinion of the Investigator, the patient is unable or unwilling to fulfill the requirements of the protocol or has a condition which would render the results uninterpretable.

5.3 Rescreening Criteria

Rescreening will only be allowed for subjects who screen fail at Visit 1 due to serum phosphorus levels outside of the protocol inclusion range (<4.0 or >8.0 mg/dL) and based on the following criteria:

- The subject must have historical serum phosphorus >4.5 mg/dL and <7.5 mg/dL during the two months immediately prior to the original screening date.
- The subject must wait a minimum of one week prior to rescreening to ensure that they would not be off phosphate binders for a period longer that the washout period described in the protocol.

Sites must obtain Sponsor approval before rescreening a subject.

5.4 Patient Withdrawal

Patients are free to discontinue the study at any time, for any reason, and without prejudice to further treatment. The Investigator may remove a patient if, in the Investigator's judgment, continued participation would pose unacceptable risk to the patient or to the integrity of the study data. Some study specific discontinuation criteria will also apply to study participants receiving tenapanor or placebo:

- **Hypophosphatemia:** Serum phosphorus ≤ 2.5 mg/dL at any time.
- **Hyperphosphatemia:**
    - Serum phosphorus ≥ 10.0 mg/dL any time after Week 2 of the 26-week treatment period
    - Serum phosphorus ≥ 9 mg/dL for two consecutive visits after Week 2 during the 26-week treatment or safety extension period
    - Serum phosphorus ≥ 9 mg/dL during the randomized withdrawal period

Patients discontinued from the randomized withdrawal period will be offered the opportunity to enter the open-label safety assessment period or be discontinued from the study and return to standard of care.

Patients in the active control group, receiving sevelamer carbonate do not have specific discontinuation criteria; they will be treated based on standard of care using the package insert for guidance.

A patient who discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. The Investigator will record the reason for early withdrawal in the eCRF.

If a patient discontinues the study, all visit procedures for Visit 23 will be completed, if possible.

5.5 Early Termination of Study

The study may be terminated at any time by the Sponsor for reasons including but not limited to the following (i) if serious side effects occur, (ii) if the Investigator does not adhere to the protocol, (iii) if, in the Sponsor's judgment, there are no further benefits to be achieved from the study, or (iv) for administrative reasons. In the event that the clinical development of the investigational product is discontinued, Ardelyx, Inc. shall inform all Investigators / institutions and IRBs overseeing the trial.

5.6 Restrictions to Patients

- For males and fertile females: Adherence to the precautions aiming at avoiding a pregnancy, including males not donating sperm, and therefore use of contraceptive methods as outlined in the Inclusion criteria (Section 5.1).

6 TREATMENT OF PATIENTS

6.1 Administration of Investigational Product

6.1.1 Identity of Investigational Product(s)

6.1.1.1 Study drug

Tenapanor hydrochloride is an amorphous, off-white to white powder. [redacted]

A matching placebo will be identically supplied in HDPE bottles.

6.1.1.2 Active control

Sevelamer carbonate will be supplied, as commercially available. Each bottle contains two-hundred seventy (270) 800 mg tablets.

6.1.2 Treatments Administered

Tablets containing 10 mg of tenapanor or corresponding placebo will be taken twice daily PO just prior to breakfast and dinner. On dialysis days, patients on HD should **not** take study drug at the meal prior to dialysis and instead take it before another meal. Each dose of one to three tablets will achieve total daily doses of 20, 40, or 60 mg tenapanor. If a meal is skipped, the dose should be taken with another meal during the day or at around the time that the meal would have been consumed.

During the randomized withdrawal period, patients in the tenapanor group will be randomized to either remain on their current dose of tenapanor or switched to placebo in a 1:1 ratio.

During the safety extension period, patients will continue with the same dose from the end of the 26-week treatment period. Titration is allowed as described for the 26-week treatment period.

Patients in the active control group will receive sevelamer carbonate for the entire 52 week study period.

6.1.3 Dose Adjustments

All patients in the tenapanor group will start at a dose of 30 mg bid. After randomization (Visit 5) to Day 183 (Visit 13), doses can be adjusted in 10 mg increments based on serum phosphorus levels and/or GI tolerability. Down-titration can go from 30 mg bid to 20 mg bid and 20 mg bid to 10 mg bid. Dose escalation can go from 10 mg bid to 20 mg bid, and 20 mg bid to 30 mg bid.

6.1.3.1 Discontinuation criteria

See Section 5.4 *Patient Withdrawal*

6.1.4 Method of Assigning Patients to Treatment Groups

The CRO or designated statistician will prepare the randomization scheme in accordance with its standard operating procedures (SOPs) and the randomization plan, which reflect Good Clinical Practice (GCP) standards.

After obtaining informed consent, patients will be allocated sequential enrollment numbers in their order of completing Screening assessments.

Patients will be randomized after the washout period 3:1 to receive tenapanor or the active control, sevelamer carbonate. Patients in the tenapanor group will be randomized a second time at the end of the 26-week treatment period to enter into the randomized withdrawal period (Visit 13) to either remain on their current dose of tenapanor or a matched placebo in a 1:1 ratio. Randomization codes will be assigned via an Interactive Response Technology (IRT).

The IRT will allocate the treatment and provide the randomization number for both the 26-week treatment period and the randomized withdrawal period. The IRT will provide the appropriate bottle ID chosen from those bottle IDs available at the study site for tenapanor and placebo only. The randomization is carried out at study level and the assigned randomization numbers and the associated bottle IDs will not be sequential within a study site. The active control will not have unique bottle ID #s.

If a patient withdraws from participation in the study, then his/her enrollment/ randomization code cannot be reused.

6.2 Investigational Product Storage and Accountability

6.2.1 Storage Conditions

The Investigator will ensure that all the study drug and active control are stored and dispensed in accordance with Food and Drug Administration (FDA) regulations concerning the storage and administration of investigational drugs.

Tablets of tenapanor and placebo should be stored in the original packaging according to the labeling. The active control should also be stored in the original packaging according to the labeling.

6.2.2 Drug Accountability

The Investigator must ensure that all drug supplies are kept in a secure locked area with access limited to those authorized by the Investigator. The Investigator or the Investigator's designee must maintain accurate records of the receipt of all study drug and active control shipped by the Sponsor or its representative, including but not limited to the date received, lot number, amount received, and the disposition of all study drug. Current dispensing records will also be maintained including the date and amount of study drug and active control dispensed and the

patient receiving the drug. All remaining study drug not required by regulations to be held by the clinical facility must be returned to Sponsor or its representative immediately after the study is completed using the study drug return form provided.

6.3 Packaging and Labeling

6.3.1 Study Drug

[redacted] Tablets of study drug should be stored in the original packaging according to the labeling.

6.3.2 Blinding Methods

The 26-week treatment period and the safety extension period are open labeled periods and study drug will not be blinded.

In the randomized withdrawal period, the treatment will be administered in a double-blind fashion. The active and placebo tablets are identical in appearance (shape, color, size, etc.).

Only the party responsible for labeling, warehousing and shipping drug supply, the study statistician, responsible for preparing the randomization list, and the IRT manager responsible ensuring drug is available at sites will have knowledge of the treatments assigned during the randomized withdrawal period.

The active control, sevelamer carbonate, will be administered as commercially packaged and used for the entire 52-week study period for patients randomized into that group.

6.4 Procedure for Breaking Randomization Code

6.4.1 Emergency Unblinding

During the course of the randomized withdrawal period, the blind is to be broken only when the safety of the patient is at risk and knowledge of the treatment is essential to the clinical management of the patient. A decision to unblind a patient must be made in concert with the Medical Monitor and the Sponsor, except in an emergency situation when the blind must be broken to determine treatment for the patient. If a patient is unblinded, the date and reason for the unblinding must be recorded on the source documents. Please refer to Section 7.3.6 for reporting requirements.

6.5 Prior and Concomitant Therapy

6.5.1 Prior Therapy

This is a study in ESRD-HD and ESRD-PD patients with hyperphosphatemia. Patients with prior therapy specified in the exclusion criteria (Section 5.2) will not be eligible for entry into the study.

6.5.2 Concomitant Therapy

The use of concomitant medications during the study, unless needed to treat an AE, should be the same as the medications used and recorded at screening and during the washout period.

All previous medication (prescription and over-the-counter), vitamin and mineral supplements, and herbs taken by the participant in the past 30 days will be recorded in the medical history section of the patient's eCRF and will include start and stop date, dose and route of administration, frequency, and indication. Medications taken for a procedure should also be included.

6.5.2.1 Prohibited Medications

The use of phosphate binders other than sevelamer carbonate used in the active control group are prohibited. Phosphate binders include but are not limited to the following:

- Sevelamer carbonate and hydrochloride (Renvela®, Renagel®)
- Lanthanum carbonate (Fosrenol®)
- Sucroferric oxyhydroxide (Velphoro®)
- Ferric citrate (Auryxia®)
- Calcium carbonate (Tums®)
- Calcium acetate (PhosLo®)

7 COLLECTION OF STUDY VARIABLES

7.1 Recording of Data

The Investigator will ensure that data are recorded in the electronic Case Report Form (eCRF) for this study. The Investigator ensures accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries. The Investigator will sign the completed eCRF and a copy of the completed eCRF will be archived.

7.2 Data Collection Prior to Enrollment

During Screening and the Wash-out Period, e.g., after signing the informed consent but prior to enrollment, the following information will be collected from every potential patient for baseline demographics as well as to assess each patient's suitability to participate in this study protocol:

- Assessment of the disease status outlined in the inclusion/exclusion criteria
- Date of birth, gender, and race
- Weight (pre-dialysis) and height (kg and cm, respectively)
- Kt/V – most recent value prior to screening
- KDQoL survey
- DSI survey (for English speakers only)
- Medical and surgical history
- Phosphate binder currently used and dose
- Physical examination
- Vital signs (pre-dialysis)
- Electrocardiogram (ECG) evaluation
- Blood sample for clinical laboratory chemistry and hematology tests, and virology laboratory tests (pre-dialysis)
- FSH and pregnancy test, if applicable
- Blood sample for Ca x P product, FGF23 and exploratory biomarkers
- Concomitant medications

7.3 Safety Variables

Safety assessments will be performed during the study and will include physical examinations, vital signs, body weights, clinical laboratory tests, electrocardiograms, and adverse event recording. Body weight, vital signs and blood collections for laboratory assessments **must** be perfomed predialysis. All other assessments may be perfomed pre-, during, or post-dialysis but should be performed at the same time at each visit. See Section 8 (Methodology/Study Visits) for a detailed schedule of procedures.

7.3.1 Physical Examination

The physical examination will include an assessment of the following items: general appearance, skin (including any pitting edema in lower legs / feet), cardiovascular, respiratory, abdomen. Any findings or absence of findings relative to each patient's physical examination will be carefully documented in the patient's eCRF.

7.3.2 Vital Signs (blood pressure and heart rate)

Blood pressure and heart rate will be obtained at all patient visits (pre-dialysis). Blood pressure, sitting systolic and diastolic blood pressure (SSBP and SDBP) will be measured after the patient has been sitting for approximately 5 minutes. All measurements will be recorded on the source document and in the eCRF.

7.3.3 Electrocardiograms

A 12-lead electrocardiogram (ECG) will be performed in the sitting or supine position (for at least 5 minutes). The ECG must be transmitted to the central ECG site (Medpace Core Lab).

The following ECG parameters will be recorded: heart rate, PR-interval, QRS (principal deflection in ECG)-duration, QT-interval (uncorrected), QTc-interval (corrected), RR-interval.

The Investigator will assess any abnormalities upon receiving an email alert from Medpace Core Lab; abnormalities will be classified as clinically significant and not clinically significant. Electrocardiographic intervals and Investigator assessment of all abnormal ECGs will be recorded on the eCRF.

Additional ECGs may be obtained if clinically indicated.

7.3.4 Clinical Laboratory Tests

Samples **must** be obtained, pre-dialysis, for the clinical laboratory tests identified in Table 7-1. A coagulation profile will only be performed on patients taking warfarin.

Other evaluations and tests performed during Screening and other time points, specified in the Schedule of Events (Section 1.3) will include:

- Serology screen, i.e., HBsAg, HCV, and HIV
- FSH test will be performed on all females at Screening
- Pregnancy test, if applicable

7.3.5 Analysis of Clinical Laboratory Tests

A certified laboratory will be used to process and provide results for the clinical laboratory tests. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug or active control.

For any laboratory test value outside the reference range that the Investigator considers clinically significant, the Investigator will:

- Repeat the test to verify the out-of-range value.
- Follow the out-of-range value to a satisfactory clinical resolution.
- Record as an AE any laboratory test value that (1) is confirmed and the Investigator considers clinically significant, or (2) that requires a patient to be discontinued from the study, or (3) that requires a patient to receive treatment, or (4) fulfills one or more SAE criteria.

Table 7-1 Clinical Laboratory Tests

Hematology[a]	Chemistry[b]	Coagulation Profile[c,d]	Serology[c]	Other[e]
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils (%) Lymphocytes (%) Monocytes (%) Basophils (%) Eosinophils (%) Platelet count	Albumin Alanine aminotransaminase (ALT) Aspartate aminotransaminase (AST) Alkaline phosphatase Bilirubin, total Bicarbonate Blood urea nitrogen (BUN) Calcium, total Chloride Creatinine Creatine kinase Glucose Magnesium Phosphorus[fj] Potassium Ca x P[j] Sodium	Prothrombin time Activated partial thromboplastin time	Hepatitis B infection Hepatitis C infection Human immunodeficiency virus	FSH[bg] Serum pregnancy[g] FGF-23[chj] Parathyroid Hormone (PTH)[c]

[a] Whole blood.
[b] Serum.
[c] Plasma.
[d] Only in people treated with Warfarin.
[e] Not part of standard clinical laboratory tests, must be specified; performed at specified time points.
[f] Serum phosphorus is also performed separately from standard clinical laboratory tests at protocol specified time points.
[g] FSH and serum pregnancy tests are performed on all females at Screening. After screening, pregnancy tests will only be performed on females of child-bearing potential unless FSH at screening indicates post-menopausal status.
[h] Both intact and c-terminus FGF-23 will be measured.
[j] Used in efficacy analyses

7.3.6 Adverse Events

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not thought to be related to the investigational product.

Patients will be monitored throughout the study for AEs, from the screening visit through the open label extension period on Day 365. All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit?", or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. In instances of well-recognized symptoms, they can be recorded as the commonly used diagnosis (e.g., fever, runny nose, and cough can be recorded as "flu"). However, if a diagnosis is known, but there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom should be recorded separately.

Adverse events that are identified at the last assessment Visit 23 (or the early termination visit) as specified in the protocol must be recorded on the AE eCRF with the status of the AE noted, and the AE must be followed until AE is resolved or stable. All events that are ongoing at this time will be recorded as ongoing on the eCRF. The procedures specified in Section 7.3.6.8 are to be followed for reporting SAEs.

7.3.6.1 Adverse Events Associated with Change in Stool Form and/or Frequency

Based on tenapanor's ability to inhibit the absorption of dietary sodium, it is known to alter stool form and frequency in some patients. For a change in stool form and/or frequency to be considered an adverse event the patient must consider the bowel movements to be "bothersome."

7.3.6.2 Recording Adverse Events

Adverse events are to be recorded on the AE page of the eCRF. Severity will be graded according to the following definitions:

- Mild: The patient experiences awareness of symptoms but these are easily tolerated or managed without specific treatment
- Moderate: The patient experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment

- Severe: The patient is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.

Action taken will be categorized as dose not changed, dose reduced, drug interrupted, drug withdrawn, required concomitant medication, required concomitant procedure and/or other.

Event outcome at resolution or time of last follow-up will be recorded as not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, fatal or unknown.

7.3.6.3 Assessment of Adverse Events

The relationship of the event to the study drug or active control should be determined by the Investigator according to the following criteria:

- Not related: The event is most likely produced by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs, and does not follow a known response pattern to the study drug/active control, or the temporal relationship of the event to study drug/active control administration makes a causal relationship unlikely
- Possibly related: The event follows a reasonable temporal sequence from the time of drug administration, and is possibly due to drug administration and cannot be reasonably explained by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs.
- 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/active control, and cannot be reasonably explained by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs.

7.3.6.4 Following Adverse Events

All (both serious and non-serious) AEs must be followed until they are resolved or stabilized, or until all attempts to determine resolution of the event are exhausted. The Investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

7.3.6.5 Discontinuation due to Adverse Events

Any patient who experiences an AE may be withdrawn at any time from the study at the discretion of the Investigator. Patients withdrawn from the study due to an AE, whether serious or non-serious, must be followed by the Investigator until the clinical outcome of the AE is determined. The AE(s) should be noted on the appropriate CRFs and the patient's progress should be followed until the AE is resolved. A decision to discontinue a patient due to an AE should be discussed with the Medical Monitor. If the AE may relate to overdose of

study treatment, the IB should be consulted for details regarding any specific actions to be taken.

7.3.6.6 Pregnancy

Female patients must be instructed to discontinue all study drugs and inform the study Investigator immediately if they become pregnant during the study.

The Investigator must report any pregnancy to [redacted] within 1 business day of becoming aware of it. The patient must be immediately discontinued from further treatment with study drug. An uncomplicated pregnancy will not be considered an AE or SAE, but all pregnancies will be followed through birth.

Pregnancies are captured if they occur in female patients or in the sexual partners of male patients from the time the patient is first exposed to the investigational product until 30 days after last exposure to the investigational product.

Any congenital abnormalities in the offspring of a patient who received study drug will be reported as an SAE. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the source documentation and reported to [redacted]

7.3.6.7 Serious Adverse Events

An SAE is any AE occurring from Screening through final study visit (Day 365), at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed in this definition. 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: SAEs require immediate reporting to [redacted]. See "Reporting Serious Adverse Events" below for details.

7.3.6.8 Reporting Serious Adverse Events

In the event of any SAE reported or observed during the study, whether or not attributable to the study drug, site personnel will report it to [redacted] within 24 hours of the knowledge of the occurrence.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the internet, send an email to [redacted] at [redacted] or call the [redacted] (phone number listed below), and fax/email the completed paper back-up SAE form to [redacted] (contact information listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available. Incoming reports are reviewed during normal business hours.

Safety Contact Information:

[redacted]

The Investigator is required to submit SAE reports to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) in accordance with local requirements. All investigators involved in trials using the same investigational product will receive any safety alert notifications for onward submission to their local IRB/IEC as required. All reports sent to investigators will be blinded.

<u>Follow-Up Reports</u>

The Investigator must continue to follow the patient until the SAE has resolved or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to [redacted] personnel via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

7.4 Efficacy Variables

Serum phosphorus will be measured at all study visits. The primary efficacy variable will be the change in s-P from the end of the 26-week treatment period (Visit 13) to the end of the randomized withdrawal period or the endpoint visit for this period. The primary efficacy analysis will be based on the difference between the tenapanor treatment and placebo treatment group in the responder population. A responder is a patient that had a serum phosphorus decrease of ≥ 1.2 mg/dL from enrollment (Day 1) to the end of the 26-week treatment period (Visit 13).

The following are the secondary variables:

- Patients reaching serum phosphorus goal levels defined as < 5.5 mg/dL during the 26-week treatment period
- Ca x P product
- iFGF23 (intact) and cFGF23 (c-terminus)
- Kidney Disease and Quality of Life survey (KDQOL)
    - Kidney Disease and Quality of Life™ (KDQOL™-36) (Copyright © 2000 by RAND and the University of Arizona)
- Dialysis Symptom Index survey (DSI)
    - The University of Pittsburgh Medical Center, VA Pittsburgh Healthcare System (Weisbord et al. J Pain Symptom Manage, 2004:27, 226-40.)

7.5 Exploratory Variables

The following exploratory variables will be collected at specified times to investigate the relationship with drug efficacy.

- Exploratory biomarker analyses (potentially in future)

Plasma and serum for future exploratory research into biomarkers related to the cardio-renal disease area and/or related to the response (i.e. distribution, safety, tolerability and efficacy) to tenapanor.

8 METHODOLOGY/STUDY VISITS

8.1 Screening (Day -21), Visit 1

At the Screening visit, the Investigator will inform each prospective patient of the nature of the study, explain the potential risks, and obtain written informed consent from the patient prior to performing any study-related procedures.

Screening evaluations will consist of the following:

- Informed consent (may be completed day(s) before Screening visit, if needed)
- Inclusion and exclusion criteria (Section 5)
- Demographics
- Height and weight (pre-dialysis)
- Medical/surgical history
- Phosphate binder used and dose
- KDQOL survey
- DSI survey (for English speakers only)
- Kt/V (most recent measurement prior to screening)
- Physical examination (Section 7.3.1)
- Vital signs (pre-dialysis) (Section 7.3.2)
- ECG evaluation (Section 7.3.3)
- Clinical laboratory tests (pre-dialysis) (Section 7.3.4)
    - Serum chemistry
    - Hematology
    - Coagulation profile (if applicable)
- FSH test and serum pregnancy test will be performed on all females
- HIV, hepatitis B and C tests
- FGF-23, Ca x P product and exploratory biomarker sample (pre-dialysis)
- Begin collecting adverse events
- Start washout of phosphate binders
- Prior/concurrent medications

Patients will be instructed not to change any concomitant medications without the approval of the Investigator. The results of the screening evaluations (available at that time) must meet the inclusion/exclusion criteria for the patient to continue to the wash-out period.

Rescreening will be allowed for subjects who screen fail at Visit 1 due to serum phosphorus levels outside of the protocol inclusion range (<4.0 or >8.0 mg/dL) and based on the criteria in Section 5.3.

8.2 Wash-out Period (Days -14, -7, and -1), Visits 2, 3 and 4

The period which patients are off binders can last up to 4 weeks. If at Visit 2, 3 or 4 (Days -14, -7 or -1) a patient's serum phosphorus is ≥ 6.0 mg/dL and not more than 10.0 mg/dL and there has been a ≥ 1.5 mg/dL increase since the screening visit (Visit 1) they can proceed to Visit 5 for enrollment; otherwise patients should proceed to the next visit. At Visit 4, if a patient's serum phosphorus does not meet the above inclusion criteria, the patient is screen failed.

The following procedures should occur at washout visits

- Review of inclusion /exclusion criteria
- Changes to medical/surgical history
- Changes to Prior/concurrent medications
- Vital signs (pre-dialysis)
- Serum phosphorus (pre-dialysis)
- Adverse event reporting

8.3 Randomization (Day 1), Visit 5

- Confirm eligibility by reviewing inclusion/exclusion criteria (Section 5)
- Body weight (pre-dialysis)
- Changes to medical/surgical history
- Physical examination
- Vital signs (pre-dialysis)
- ECG evaluation
- Clinical laboratory tests (pre-dialysis)
- Serum pregnancy test, if applicable
- FGF-23, Ca x P product and exploratory biomarker sample (pre-dialysis)
- Dispense study drug or active control
- Adverse event reporting
- Review prior/concurrent medications

8.4 Treatment Period (Days 8 and 15 ± 5), Visits 6 and 7

- Vital signs (pre-dialysis)
- Serum phosphorus (pre-dialysis)

- Adverse event reporting
- Return/accountability of study drug or active control (Day 8, Visit 6 only)
- Dispense study drug (Day 8, Visit 6 only), if applicable
- Review concurrent medications

8.5 Treatment Period (Days 29 ± 5 and 57 ± 7), Visits 8 and 9

- Vital signs (pre-dialysis)
- Return/accountability of study drug or active control
- Dispense study drug or active control, if applicable
- Serum phosphorus (pre-dialysis)
- Adverse event reporting
- Review concurrent medications

8.6 Treatment Period (Day 85 ± 7), Visit 10

- Body weight (pre-dialysis)
- KDQOL survey
- DSI survey (for English speakers only)
- Vital signs (pre-dialysis)
- ECG evaluation
- Clinical laboratory tests (pre-dialysis)
- Serum pregnancy test, if applicable
- FGF-23, Ca x P product and exploratory biomarker sample (pre-dialysis)
- Return/accountability of study drug or active control
- Dispense study drug or active control, if applicable
- Adverse event reporting
- Review concurrent medications

8.7 Treatment Period (Days 120 and 155 ± 7), Visits 11 and 12

- Vital signs (pre-dialysis)
- Return/accountability of study drug or active control
- Dispense study drug or active control, if applicable
- Serum phosphorus (pre-dialysis)
- Adverse event reporting
- Review concurrent medications

8.8 End of 26-week Treatment Period and start of Randomized Withdrawal Period (Day 183 ± 7), Visit 13

- Randomization #2
- Body weight (pre-dialysis)
- KDQOL survey
- DSI survey (for English speakers only)
- Physical Examination
- Vital signs (pre-dialysis)
- ECG evaluation
- Clinical laboratory tests (pre-dialysis)
- Serum pregnancy test, if applicable
- FGF-23, Ca x P product and exploratory biomarker sample (pre-dialysis)
- Return/accountability of study drug or active control
- Dispense study drug or active control, if applicable
- Adverse event reporting
- Review concurrent medications

8.9 Randomized Withdrawal Period (Days 197, 211, 225, 239 and 253 ± 7), Visits 14, 15, 16, 17 and 18

Subjects in the active control group do not have Visits 14, 16 and 18.

- Vital signs (pre-dialysis)
- Serum phosphorus (pre-dialysis)
- FGF-23, Ca x P product and exploratory biomarker sample (Days 211 and 239 ± 5, Visits 15 and 17 only)
- Dispense study drug or active control at Visits 15 and 17 only, if applicable
- Return/accountability of study drug or active control
- Adverse event reporting
- Review concurrent medications

8.10 End of Randomized Withdrawal Period and start of Safety Extension Period (Day 267 ± 7), Visit 19

- Body weight (pre-dialysis)
- KDQOL survey
- DSI survey (for English speakers only)
- Physical Examination
- Vital signs (pre-dialysis)

- ECG evaluation
- Clinical laboratory tests (pre-dialysis)
- Serum pregnancy test, if applicable
- FGF-23, Ca x P product and exploratory biomarker sample (pre-dialysis)
- Return/accountability of study drug or active control
- Dispense study drug or active control, if applicable
- Adverse event reporting
- Review concurrent medications

8.11 Safety Extension Period (Days 281, 309, 337 ± 7), Visits 20, 21, 22

- Pre-dialysis body weight (Day 337, Visit 22 only)
- Vital signs (pre-dialysis)
- Serum phosphorus (pre-dialysis)
- Return/accountability of study drug or active control
- Dispense study drug or active control, if applicable
- Adverse event reporting
- Review concurrent medications

8.12 End of Study (Day 365 ± 7), Visit 23

- Body weight (pre-dialysis)
- KDQOL survey
- DSI survey (for English speakers only)
- Physical Examination
- Vital signs (pre-dialysis)
- ECG evaluation
- Clinical laboratory tests (pre-dialysis)
- Serum pregnancy test, if applicable
- FGF-23, Ca x P product and exploratory biomarker sample (pre-dialysis)
- Return/accountability of study drug or active control
- Adverse event reporting
- Review concurrent medications

8.13 Unscheduled visits

Unscheduled visits, for missed scheduled visits or safety or tolerability related reasons are allowed. Procedures performed are at the discretion of the Investigator.

8.14 Withdrawal Procedures

In the event of a patient's withdrawal, the Investigator will make every effort to complete all assessments performed at End-of-treatment visit on Day 365 (Visit 23). Withdrawn patients will be followed until resolution of any AEs or until the unresolved AEs are judged by the Investigator to have stabilized.

For the withdrawal criteria see Section 5.4.

8.15 Total Blood Volume Required for Study

Table 8-1 Approximate Blood Volume per Completed Patient

Test	Number of Samples	Volume (mL)	Total (mL)
Serology and FSH test (serum)	1	5	5
Hematology (blood)	6	3	18
Chemistry (serum) (includes serum pregnancy test)	6	7	42
Phosphorus / Calcium (serum)[#]	17	7	119
PTH (plasma)	8	4	32
FGF-23 (plasma)	8	8	64
Exploratory biomarker sample (serum and plasma)	8	13	104
Total volume	--	--	**384**

[#]Separate sample is only taken at specified times when no chemistry sample is taken

8.16 Protocol Deviations

Patients must fully meet the following criteria in order to enroll in the study. In keeping with regulatory requirements, Ardelyx does not grant protocol waivers to inclusion/exclusion criteria.

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the patient, Investigator, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria
- Failure to comply with dispensing or dosing requirements
- Missed or out-of-window visits
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, medical history; either tests not done, incorrect tests done, or not done within the time frame specified in the protocol

- Procedural deviations such as incorrect storage of study drug, failure to update the ICF when new risks become known, failure to obtain Institutional Review Board (IRB) approvals for the protocol and ICF revisions

A process for defining and handling protocol deviations will be established. Protocol deviations that effect the safety of a patient requires immediate notification of the Medical Monitor and Sponsor. The Investigator is responsible for seeing that any known protocol deviations are recorded and handled as agreed.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Plan

A formal statistical analysis plan (SAP) is provided separately. No changes are expected for the primary and secondary analyses. If the language in this protocol and the language in the SAP differ, the SAP governs. If additional analyses are performed or changes are made to the planned analyses after unblinding of the study data, such deviations will be documented in the clinical study report.

9.2 Determination of Sample Size

Approximately five hundred sixty (560) male and female patients with end stage renal disease (ESRD) on chronic maintenance hemodialysis (HD) 3 times a week for a minimum of 3 months or peritoneal dialysis (PD) for a minimum of 6 months will be enrolled in this study. Patients will be randomized in a 3:1 ratio to receive either tenapanor (~420 patients) or active control (~140 patients). Those patients in the tenapanor group will be randomized at the end of the 26-week treatment period to enter into the randomized withdrawal period to either remain on their current dose of tenapanor or placebo in a 1:1 ratio.

For the primary efficacy analysis, a sample size of 146 patients (73 patients/group) in the 12-week randomized withdrawal period is expected to provide more than 95% power to detect a difference between tenapanor and placebo treatment in the change in serum phosphorus from the end of the 26-week treatment period to the end of the 12-week randomized withdrawal period or the endpoint visit for this period, between the tenapanor treatment and placebo. This calculation is based on a two-sample t-test with a two-sided significance level of α=0.05, an assumed treatment difference of 1.0 mg/dL and a common standard deviation of 1.6 mg/dL. This sample size (560) allows for a 30% dropout rate, meaning 30% of patients will not complete the 26-week treatment period. This sample size also assumes at least 50% of patients in the tenapanor group will be considered responders in the 26-week treatment period, i.e., patients who achieves at least a 1.2 mg/dL reduction from baseline to the end of the 26-week treatment period.

9.3 Analysis Sets

Four analysis sets are defined for this study: safety analysis set, intent to treat (ITT) analysis set, efficacy analysis set and per-protocol (PP) analysis set. These analysis sets will be determined for each study period separately (if applicable). The safety analysis set will be defined based on all patients enrolled in this study. All other three analysis sets will be defined based on those patients who are randomized to receive tenapanor in the 26-week treatment period.

Safety Analysis Set:

All patients who receive at least one dose of study drug (tenapanor or placebo) or active control for the individual study period will be included in the safety analysis set. Such patients will be analyzed according to the treatment actually received.

Intent to Treat (ITT) Analysis Set:

All patients who meet the study entry inclusion/exclusion criteria, receive at least one dose of tenapanor or placebo, and have at least one post treatment serum phosphorus assessment for the individual study period will be included in the ITT analysis set. For the 12-week randomized withdrawal period, patients will be analyzed according to the treatment group into which they were randomized. The ITT analysis set will be used for the analysis of all efficacy variables.

Efficacy Analysis Set:

All patients who meet the study entry inclusion and exclusion criteria, receive at least one dose of tenapanor during the 26-week treatment period, complete the 26-week treatment period, and achieve at least a 1.2 mg/dL reduction in serum phosphorus from baseline to the end of the 26-week treatment period will be included in the efficacy analysis set. The efficacy analysis set will be used for the primary efficacy analysis.

Per-Protocol Analysis Set:

All patients in the ITT analysis set who complete the 12-week randomized withdrawal period as planned with no major protocol deviations that impact the primary efficacy variable. The per-protocol (PP) analysis set will be used for sensitivity analyses to support the primary and key secondary efficacy analyses. Patients in the PP analysis set will be determined prior to the database lock or unblinding of the study data.

9.4 Statistical Methods

9.4.1 General Approach

Descriptive statistics including the number of observations, mean, standard deviation, median, minimum, and maximum will be presented for continuous variables. Frequency and percentage of patients will be presented for categorical variables. Continuous variables will be analyzed using analysis of variance (ANOVA) or analysis of covariance (ANCOVA). Categorical variables will be analyzed using a Cochran-Mantel-Haenszel (CMH) test or a Pearson's Chi-square test.

Safety analyses will be performed on all patients enrolled in this study, while efficacy analyses will be performed only on those patients who are randomized to receive tenapanor

in the 26-week treatment period (i.e., patients treated with active control will not be included in any efficacy analyses).

9.4.2 Baseline Descriptive Statistics

Baseline characteristics, including demographics, disease characteristics, prior/concomitant medications, and medical/surgical history will be summarized by treatment (including dose, if applicable) group and overall for each analysis set. These summaries will be provided for each study period separately.

9.4.3 Primary Efficacy Analysis

The primary efficacy variable is the change in s-P from the end of the 26-week treatment period (Visit 13) to the end of the 12-week randomized withdrawal period (Visit 19) or the endpoint visit for this period. An endpoint visit is defined as the last visit with an s-P assessment during the randomized withdrawal period. The primary interest of this study is the difference between the tenapanor treatment and placebo treatment group in the mean change (w.r.t. the primary efficacy variable) in the responder population (the efficacy analysis set). A responder is a patient that had a serum phosphorus decrease of $\geq$ 1.2 mg/dL from enrollment (Day 1) to the end of the 26-week treatment period (Visit 13). The primary efficacy variable will be analyzed using an ANCOVA model. The model includes fixed effects for treatment, pooled investigator site, and the baseline s-P value as a continuous covariate. The baseline for this analysis is defined as the s-P value at the end of 26-week treatment period. Within the framework of this model, the difference between the tenapanor treatment and placebo treatment in the mean change from the end of the 26-week treatment period to the end of the 12-week randomized withdrawal period (or the endpoint visit for this period) will be estimated. The corresponding two-sided 95% CI and the p-value for the treatment difference will also be presented. Statistical significance will be declared if the estimated difference between the tenapanor treatment and placebo treatment in the mean change is negative (i.e., $<$ 0) and the corresponding two-sided p-value is $\leq$ 0.05.

9.4.4 Secondary Efficacy Analyses

9.4.4.1 Key Secondary Efficacy Analyses

The analysis method described for the primary efficacy variable in Section 9.4.3 will be performed as follows:

- in the ITT analysis set
- to compare the individual doses of tenapanor and placebo in the ITT analysis set – from high dose to low dose
- to compare the individual doses of tenapanor and placebo in the efficacy analysis set – from high dose to low dose

A sequential testing procedure will be used to control the family-wise type I error rate associated with the key secondary efficacy analyses. Specifically, the primary efficacy analysis will be performed at the 5% significance level. If statistical significance is declared for this analysis, then the first key secondary efficacy analysis listed in this section will be performed at the 5% level. If statistical significance is declared for this analysis, then the next key secondary efficacy analysis will be performed at the 5% level. This procedure continues until one of the key secondary efficacy analysis in the list results in a p-value >5%. Statistical significance will be declared for secondary efficacy analyses up to this point in the list.

9.4.4.2 Other Secondary Efficacy Analyses

The change in s-P from baseline to the end of 26-week treatment period will be analyzed using an ANCOVA model with effects for pooled investigator site, and the baseline s-P value as a continuous covariate. The LS-mean of the change will be presented with the corresponding two-sided 95% CI and p-value.

The proportion of patients reaching serum phosphorus goal levels of <5.5 mg/dl at each visit during the 26-week treatment period will be estimated with asymptotic 95% CI.

ANCOVA will be performed for the change from baseline at each visit for the following variables:

- Ca x P product
- iFGF23 (intact) and cFGF23 (c-terminus), both on a logarithmic scale
- Kidney Disease Quality of Life survey (KDQoL)
- Dialysis Symptom Index survey (DSI)

The ANCOVA model includes fixed effects for treatment (including dose, if applicable) group, pooled investigator site, and the baseline value (defined for the individual study period) as a continuous covariate. Specifically,

- for the 26-week treatment period and safety extension period, the LS-mean of the change will be presented with the corresponding two-sided 95% CI and p-value. For iFGF23 and cFGF23, the back-transformed point estimate and 95% CI will be provided.
- for the randomized withdrawal period, the treatment group difference between tenapanor and placebo in the mean change will be estimated with the corresponding two-sided 95% CI and p-value. For iFGF23 and cFGF23, the back-transformed point estimate and 95% CI will be provided.

All secondary efficacy analyses described in this section will be descriptive and no multiplicity adjustment will be made for these analyses.

9.4.5 Procedures for Handling Missing Serum Phosphorus Data

In the completed clinical study TEN-02-201 (with similar study design and primary efficacy variable but different treatment durations) conducted by Ardelyx, the rate of missing s-P data was 6.25% (5/80) at both week-2 and week-4 during the 4-week randomized withdrawal period. The rate of missing s-P data during the randomized withdrawal period in the current study is expected to be in the similar range for the first 4 weeks and higher than 6.25% thereafter (i.e., from week-4 to week-12, no information about such data from literature or other similar clinical trials). Since the last observation carried forward (LOCF) method (stated below) will be used for the primary efficacy analysis, the missing s-P data during the randomized withdrawal period is expected to have very limited impact on the power of the analysis for the current study.

An endpoint visit for the primary efficacy analysis is defined as the last visit with an s-P assessment during the randomized withdrawal period, which amounts to imputing the missing s-P data at Week-12 of the randomized withdrawal period using the LOCF method such that each patient's s-P value at the endpoint visit represents the patient's last experience while receiving study treatment. Assuming that more placebo patients will drop out early because of a lack of efficacy during the randomized withdrawal period, and as such, LOCF will tend to underestimate the true effect of the drug relative to placebo providing a conservative estimate of the drug's effect.

To support the primary efficacy analysis (LOCF method), a sensitivity analysis will be performed using a mixed-effects model for repeated measures (MMRM). Specifically, the dependent variable for the MMRM model will be the change in s-P from the end of the 26-week treatment period (Visit 13) to each visit during the 12-week randomized withdrawal period, and the MMRM model includes fixed effects of treatment, pooled investigator site, visit (Visit 14 through Visit 19), treatment-by-visit interaction, and the baseline s-P value as a continuous covariate. The baseline is defined as the s-P value at the end of 26-week treatment period. The covariance matrix for the repeated measures will be assumed to be unstructured. Within the framework of this model, the difference between the tenapanor treatment and placebo treatment in the mean change from the end of the 26-week treatment period to week-12 of the 12-week randomized withdrawal period will be estimated. The corresponding two-sided 95% CI and the p-value for the treatment difference will also be presented.

An endpoint visit (the LOCF method) will also be used for other efficacy analyses, if applicable. All other efficacy analyses will be performed based on the observed data.

9.4.6 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 patients 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 patients per pooled investigator site. The size of a pooled investigator site would generally depend on the enrollment size for each individual investigator site. The pooled investigator sites will be used in all applicable analyses where adjustment for investigator effect is desired.

9.4.7 Visit Windows

No analysis visit windows will be formally defined. The schedule of events in Section 1.3 details the intended collection of study variables at specified visits. Should additional data be collected between scheduled visits, these data will be included in the patient data listings but ignored for analyses purposes, unless the additional data is the last data collected during each study period.

9.4.8 Safety Analyses

Safety analyses include summaries for adverse events, safety laboratory tests, vital signs, body weights, 12-lead ECGs, and physical examinations. These summaries will be provided for each study period separately.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables and listings will be provided by system organ class and preferred term for each treatment (including dose, if applicable) group for treatment-emergent adverse events (TEAEs). Actual values and change from baseline values for clinical laboratory tests, vital signs, body weights, and ECGs will be summarized by treatment (including dose, if applicable) group for each visit. The number and percentage of patients in each physical examination category will be presented by treatment (including dose, if applicable) group for each visit.

10 ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will provide direct access to source data and documents for the Sponsor or its designee conducting study-related monitoring and/or audits, IRB/ Independent Ethics Committee (IEC) review, and regulatory review. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP (Good Clinical Practice), guidelines of the International Conference on Harmonization (ICH), and any application regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at any clinical site.

The Investigator must inform the study patient that his/her study-related records may be reviewed by the above individuals without violating the patient's privacy of personal health information in compliance with regulations of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to clinical Investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the Investigator and IRB. By signing this protocol, the Investigator affirms to the Sponsor that the Investigator will maintain, in confidence, information furnished to him or her by the Sponsor and will divulge such information to the IRB under an appropriate understanding of confidentiality with such board.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor or its designee will implement and maintain quality control and quality assurance procedures with written SOPs to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

11.1 Conduct of Study

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof (Tokyo 2004), and in accordance with the FDA Code of Federal Regulations (21 CFR Parts 11, 50, 54, 56, 312) and the International Conference on Harmonization (ICH) Guidelines on good clinical practice (ICH E6 R2). Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by an IRB or IEC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB, except when necessary to eliminate immediate hazards to the patient. Any deviation may result in the patient having to be withdrawn from the study, and may render that patient non-evaluable.

11.2 Protocol Amendments

Only the Sponsor may modify the protocol. All amendments that have an impact on patient risk or the study objectives, or require revision of the ICF, must receive approval from the IRB prior to their implementation. Should the protocol changes be significant i.e., where there are changes in the existing protocol that significantly affect safety of patients, scope of the investigation, or scientific quality of the study, the Sponsor must submit the protocol to the FDA prior to the protocol amendment being implemented.

11.3 Monitoring of Study

The Investigator will permit the site monitor to review study data as frequently as is deemed necessary to ensure data are being recorded in an adequate manner and protocol adherence is satisfactory.

The Investigator will provide access to the source documents or provide certified copies of the medical records for the monitor to verify eCRF entries. The Investigator is expected to cooperate with the Sponsor/designee in ensuring the study adheres to GCP requirements.

The Investigator may not recruit patients into the study until Sponsor or its designee has conducted a detailed review of the protocol and eCRF with the site staff. With agreement of Sponsor, attendance at an Investigator meeting may fulfill this requirement.

11.4 ETHICS

11.5 Institutional Review Board/Independent Ethics Committee Approval

11.5.1 Ethics Review Prior to Study

The Investigator will ensure that the protocol and consent form are reviewed and approved by the appropriate IRB prior to the start of any study procedures. The IRB will be appropriately constituted and will perform its functions in accordance with FDA regulations, ICH GCP guidelines, and local requirements as applicable.

11.5.2 Ethics Review of other Documents

In addition, the IRB will approve all protocol amendments (except for Sponsor-approved logistical or administrative changes), written informed consent documents and document updates, patient recruitment procedures, written information to be provided to the patients, available safety information, information about payment and compensation available to patients, the Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB and regulatory authority as applicable.

11.6 Written Informed Consent

The nature and purpose of the study will be fully explained to each patient (or the patient's legally responsible guardian). The patients must be given ample time and opportunity to inquire about details of the trial, to have questions answered to their satisfaction, and to decide whether to participate. Written informed consent must be obtained from each patient (or guardian) prior to any study procedures being performed.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Reporting and Case Report Forms

12.1.1 Case Report Forms

The Investigator will be provided with eCRFs, and will ensure all data from patient visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign the eCRFs to verify the integrity of the data recorded.

12.1.2 Laboratory Data

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to trial start. If a central laboratory has been selected to conduct any or all tests, it is essential all samples be analyzed at that laboratory. The Investigator must maintain source documents such as laboratory reports and complete history and physical examination reports.

12.1.3 Retention of Source Documents

The Investigator must maintain source documents such as laboratory reports, x-rays, ECGs, consultation reports, and complete history and physical examination reports.

12.2 Retention of Essential Documents

Essential documents should be maintained for at least 11 years based upon the Sponsor's requirements and may be required to be maintained longer based upon applicable regional regulatory requirements. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents. Should the Investigator/institution not be able to maintain the records for this period of time, the Investigator/institution must inform the Sponsor in writing, via certified mail, at least 90 days prior to the destruction of any study documents, so that the Sponsor has the option, at the Sponsor's expense, to have the records stored for a longer period of time. It is the responsibility of Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

13 ADMINISTRATIVE INFORMATION

[redacted]

14 REFERENCES

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–117.

Campanelli PC, Martin EA, Rothgeb JM. The use of respondent and interviewer debriefing studies as a way to study response error in survey data. The Statistician. 1991;40:253–264.

Ericsson KA, Simon HA. Verbal reports as data. Psychological Review. 1980;87:215–250.

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

Lindsay RM, Heidenheim PA, Nesrallah G, Garg AX, Suri R. Minutes to recovery after a hemodialysis session: a simple health-related quality of life question that is reliable,valid, and sensitive to change. Clin J Am Soc Nephrol. 2006;1:952–959.

Weisbord SD, Fried LF, Arnold RM, Rotondi AJ, Fine MJ, Levenson DJ, Switzer GE. Development of a symptom assessment instrument for chronic hemodialysis patients: the dialysis symptom index. J Pain Symp Manage. 2004;27:226–240.

Eknoyan G, Lameire N, Barsoum R, Eckardt KU, Levin A, Levin N, Locatelli F, MacLeod A, Vanholder R, Walker R, Wang H. The burden of kidney disease: improving global outcomes. Kidney Int. 2004;66(4):1310–1314.

Waheed AA, Pedraza F, Lenz O, Isakova T (2013) Phosphate control in end-stage renal disease: barriers and opportunities. Nephrology, Dialysis, Transplantation 2013;0:1-8.

KDIGO, Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney International 2009;76(Suppl 113):S1-S130

dDOPPS Annual Report of the Dialysis Outcomes and Practice Patterns Study: Hemodialysis Data 1999-2008. Arbor Research Collaborative for Health, Ann Arbor, MI. Available from: http://www.dopps.org/annualreport/archives/DOPPSAR2010/index.htm

15 SIGNATURES

15.1 Investigator Signature

I agree to conduct the study outlined above according to the terms and conditions of the protocol, GCP guidelines, and with applicable regulatory requirements. All information pertaining to the study will be treated in a confidential manner.

Investigator's Signature _____

Investigator's Printed Name	
Investigational Site or Name of Institution	

Date_____

15.2 Sponsor Signature

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

[redacted]

Date