Clinical Study Protocol

A Long-Tern, Open Label Study to Evaluate the Ability of Tenapanor Alone or in Combination with Sevelamer to Treat to Goal Serum Phosphorus in Patients with End-Stage Renal Disease on Dialysis (NORMALIZE)

Protocol No.: TEN-02-401

15April 2019

NCT03988920

CLINICAL STUDY PROTOCOL

Study TEN-02-401

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Protocol No.: TEN-02-401

Edition No.: 1

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Sponsor:
Ardelyx, Inc.
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1 GENERAL INFORMATION

1.1 Study Administrative Structure

A Long-Term, Open Label Study to Evaluate the Ability of Tenapanor Alone or in Combination with Sevelamer to Treat to Goal Serum Phosphorus in Patients with End-Stage Renal Disease on Dialysis (NORMALIZE).

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

1.2 Synopsis

Protocol Title: A Long-Term, Open Label Study to Evaluate the Ability of Tenapanor Alone or in Combination with Sevelamer to Treat to Goal Serum Phosphorus in Patients with End-Stage Renal Disease on Dialysis (NORMALIZE).

Sponsor: Ardelyx, Inc.

Study Phase: Phase 3

Objectives: The primary objective of this study is:

- To evaluate the ability of tenapanor alone or in combination with sevelamer to achieve serum phosphorus concentration (sP) within the population reference range (sP $\geq$2.5 and $\leq$4.5 mg/dL) in patients with end-stage renal disease on dialysis with hyperphosphatemia (>4.5 mg/dL).

The secondary objectives of this study are:

- To compare the phosphorus lowering effect of tenapanor and sevelamer alone in patients with sP >4.5 mg/dL to patients treated with a combination of tenapanor and sevelamer.
- To evaluate the effect of tenapanor alone and in combination with sevelamer on the proportion of patients reaching serum phosphorus targets defined as $\leq$4.5 mg/dL.
- To evaluate the effect of the addition of tenapanor to patients taking sevelamer on the percentage reduction in the sevelamer dose.
- To evaluate the effect of tenapanor alone and in combination with sevelamer on intact fibroblast growth factor 23 (iFGF23).
- To evaluate the effect of tenapanor alone and in combination with sevelamer on the Kidney Disease Quality of Life (KDQoL) survey.
- To evaluate the effect of tenapanor alone and in combination with sevelamer on the Dialysis Symptom Index (DSI) survey (for English speakers only).
- To compare the long-term safety of tenapanor alone and in combination with sevelamer.

The exploratory objectives of this study are:

- To evaluate the effect of tenapanor alone and in combination with sevelamer on PTH, CRP, aldosterone and other cardio-renal biomarkers (These data may not be part of the study report.)
- To collect and store plasma/serum for future exploratory research into serum/plasma biomarkers related to cardio-renal disease and/or mineral metabolism or that may influence the response

	(i.e. distribution, metabolism, safety, tolerability, and efficacy) to tenapanor. (These data will not be part of the study report.)
Number of Sites:	40-60 clinical sites in the US
Number of Patients	Approximately 150-200 patients with ESRD on hemodialysis (HD) or peritoneal dialysis (PD).
Study Design	Patients who complete the TEN-02-301 study (PHREEDOM) may be eligible to enroll into TEN-02-401 (NORMALIZE). Patients will be required to sign an ICF and meet all inclusion/exclusion criteria. No baseline assessments will be performed as part of this protocol; all baseline data for TEN-02-401 will be taken from the TEN-02-301 End of Treatment (EOT) visit. Patients from the TEN-02-301 tenapanor arm will either receive only tenapanor or be given sevelamer in addition to tenapanor based on their sP. Patients from the TEN-02-301 sevelamer arm will be given tenapanor in addition to their sevelamer dose and the sevelamer dose will then be adjusted based on their sP following a protocol-specified dose titration schedule. Patients will be monitored for safety and efficacy with in-office and telephone visits for up to an additional 18 months. All study visits 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 and blood collections for laboratory assessments **must** be performed pre-dialysis. All other assessments may be performed pre-, during, or post-dialysis but should be performed at the same time at each visit. For patients receiving PD, visits should be performed on the same day each week, if possible. **Tenapanor Arm** The dosing regimens described below for sevelamer are for guidance to the Investigators. Investigators have flexibility to dose sevelamer, TID, BID or QD based on their experience with each patient or as per package insert. Dosing regimens can be adjusted based on the most recent sP laboratory data (central laboratory data or standard of care local laboratory data). If patients are in the tenapanor arm (from the TEN-02-301 study), sevelamer will be added as described below: • sP $\geq$2.5 and $\leq$4.5 mg/dL: no addition of sevelamer. • sP >4.5 and $\leq$5.0 mg/dL: add one 800 mg tablet QD. • sP >5.0 and $\leq$5.5 mg/dL: add one 800 mg tablet BID. • sP >5.5 mg/dL: add one 800 mg tablet TID.

If sP is still greater than or becomes >4.5 mg/dL at a subsequent visit, sevelamer dose can be increased in a stepwise manner as described below:

- sP >4.5 and ≤5.0 mg/dL: add one 800 mg tablet to the existing regimen.
- sP >5.0 and ≤5.5 mg/dL: add two 800 mg tablets to the existing regimen.
- sP >5.5 mg/dL: add three 800 mg tablets each day (800 mg TID) to the existing regimen.

The maximum dose of sevelamer should be based on standard of care, the sevelamer package insert, and the Investigator's experience with each patient.

If sP <2.5 mg/dL at any visit

- Sevelamer dose can be lowered by one 800 mg tablet TID, or as appropriate, based on current regimen; Investigators have flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert.
- If patient is not taking sevelamer then tenapanor dose can be lowered by one 10 mg tablet BID, unless already at tenapanor 10 mg BID, then can dose tenapanor 10 mg QD

Sevelamer Arm

If patients are from the TEN-02-301 sevelamer arm, tenapanor dose will be added based on their baseline sP as described below. Investigators may decrease or increase the tenapanor dose based on sP levels and/or GI tolerability in 10 mg increments to a minimum of 10 mg QD or a maximum of 30 mg BID, not more than once daily. Dosing regimens can be adjusted based on the most recent sP laboratory data (central laboratory data or standard of care local laboratory data).

- sP >2.5 and ≤3.5 mg/dL: add three 10 mg tablets of tenapanor QD and Sevelamer dose can be lowered by one 800 mg tablet TID.
- sP >3.5 and ≤4.5 mg/dL: add three 10 mg tablets of tenapanor QD
- sP ≥4.5: add three 10 mg tablets of tenapanor BID

If sP >4.5 mg/dL at next visit

- If on QD tenapanor, add three 10 mg tenapanor tablets to a maximum of 30 mg tenapanor BID. If on 30 mg tenapanor BID follow sevelamer dose regimen changes described below
- Sevelamer dose can be increased by at least one 800 mg tablet at the largest meal and up to one 800 mg tablet TID; Investigators have flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert.

If sP <2.5 mg/dL at any visit

- Sevelamer dose can be lowered by one 800 mg tablet TID; Investigators have flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert.
- If patient is not taking sevelamer then tenapanor dose can be lowered by one 10 mg tablet BID, unless already at tenapanor 10 mg BID, then can dose tenapanor 10 mg QD

For all subjects enrolled in TEN-02-401, tenapanor will be taken either once (QD; just prior to dinner or largest meal of the day) or twice daily (BID; 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 previous or next meal after dialysis. Sevelamer will be taken as per package insert.

Investigators may decrease or increase the tenapanor dose based on sP levels and/or GI tolerability in 10 mg increments to a minimum of 10 mg BID or a maximum of 30 mg BID not more than once daily.

Laboratory assessments will be measured at every visit (Weeks 1, 2, 3, 4, 6 and 8 and Months 3, 6, 9, 12, 15 and 18) using a central laboratory.

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.

Patient Selection Criteria:

Inclusion Criteria:

1. Signed and dated informed consent prior to any study specific procedures.
2. Completion of TEN-02-301(PHREEDOM)
3. Women 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 (from TEN-02-301 study), or 60 years of age or greater.
   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.

d. Male partner who is sterile or using a condom with spermicide.

4. Male participants 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 30 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. Able to understand and comply with the protocol.

Exclusion Criteria:

1. 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.
2. Life expectancy <12 months.
3. 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 800 mg sevelamer carbonate tablets.

Statistical Analyses:

Analysis Populations:

Safety Analysis Set:

All patients who receive at least one dose of study drug (tenapanor or sevelamer) in the study. The safety analysis set will be used for the analysis of safety variables.

Full Analysis Set (FAS):

All patients who meet the study entry inclusion/exclusion criteria, receive at least one dose of study drug (tenapanor or sevelamer), and have at least one post-baseline sP assessment in the study. The FAS will be used for the analysis of efficacy variables.

Efficacy Analyses:

All efficacy variables will be descriptively summarized at each visit for the FAS and each TEN-02-301 treatment arm (tenapanor or sevelamer). Descriptive summaries of sP variables will also be repeated for FAS subjects with a baseline sP >4.5 mg/dL.

For response endpoints, the response rate at each post-baseline visit will be estimated with asymptotic 95% confidence interval (CI) for each TEN-02-301 treatment arm. Inferential analyses of sP endpoints will be performed for comparisons of phosphorus-lowering effect between monotherapy (tenapanor and sevelamer alone) and combination therapy (tenapanor combined with sevelamer) unless the sample size in each monotherapy treatment group is less than 15. Inferential analyses of other endpoints may be performed as suggested by the data.

Analyses are described in Section 9 and will be detailed in the statistical analysis plan (SAP).

Safety Analyses:

All safety measures will be descriptively summarized for the Safety Analysis Set and each TEN-02-301 treatment arm (tenapanor or sevelamer).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class and preferred term.

Actual values and change from baseline values for clinical laboratory tests, vital signs, body weights, and ECGs will be descriptively summarized by visit. The number and percentage of patients in each physical examination category will be presented by visit.

1.3 Schedule of Events

Study Day	Base-line*	W1 ± 2 days	W2 ± 2 days	W3 ± 2 days	W4 ± 2 days	W6 ± 2 days	W8 ± 2 days	M 3 ± 2 weeks	M 4 ± 2 weeks	M 5 ± 2 weeks	M 6 ± 2 weeks	M 7 ± 2 weeks	M 8 ± 2 weeks	M 9 ± 2 weeks	M 10 ± 2 weeks	M 11 ± 2 weeks	M 12 ± 2 weeks	M 13 ± 2 weeks	M 14 ± 2 weeks	M 15 ± 2 weeks	M 16 ± 2 weeks	M 17 ± 2 weeks	M 18 EOT
Visit	V1	V2	V3	V4	V5	V6	V7	V8	T1	T2	V9	T3	T4	V10	T5	T6	V11	T7	T8	V12	T9	T10	V13
ICF	X																						
I/E Criteria	X																						
Med History[m]	X																						
BW, Ht, Kt/V[l]	X							X			X			X			X			X			X
Physical Exam	X																						X
Vital Signs[a]	X							X			X			X			X			X			X
ECG	X																						X
Clin Lab Tests[b]	X							X			X			X			X			X			X
Pregnancy Test[c]	X																						X
Drug Dispense[j]	X	X[j]	X[j]	X[j]	X[j]	X	X[j]	X			X			X			X			X			
Drug Return[k]		X	X	X	X	X	X	X			X			X			X			X			X
KDQoL/DSI[d]	X										X						X						X
s-Phosphorus[e]	X	X	X	X	X	X	X	X			X			X			X			X			X
FGF23	X							X			X			X			X			X			X
Exploratory Biomarkers[f]	X							X			X			X			X			X			X
AE Assess[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ConMeds[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* All baseline procedures, except informed consent and I/E criteria will come from the TEN-02-301 EOT visit; V= visit at office or dialysis center; T= telephone visit; W= week, weekly visits are after a short dialysis interval and have a ± window of 2 days ; M= month; monthly visits have a ± window of 2 weeks.

[a] If collected as part of standard of care, that data can be used and includes blood pressure and pulse.

[b] Clinical laboratory tests: All blood collections are performed pre-dialysis.. See Table 7-1 for list of tests.

[c] Pregnancy tests (serum) will only be performed on women of child-bearing potential.

[d] 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.

[e] Serum phosphorus will be measured by a central laboratory.

[f] Serum and plasma samples will be collected at the same time as the clinical laboratory evaluation and sent to the central laboratory for storage.

[g] AEs and SAEs will be collected from consenting to the end of study.

[h] Guidelines will be provided to limit the amount of concomitant medication information collected.

[j] Investigators can adjust doses of tenapanor or sevelamer between visits via telephone. Sevelamer can be re-dispensed at Visits 2, 3, 4, 5, and 8 if dose permits.

[k] Sevelamer can be re-dispensed, if enough drug is left until the next visit. Drug accountability is also performed.

[l] Body weight is for HD patients only, height from TEN-02-301, and Kt/V can be taken from most recent standard-of-care assessment.

[m] Major medical conditions taken from TEN-02-301.

1.4 List of Abbreviations

Abbreviation	Definition
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 CRP	Electronic case report form c-reactive protein
CSR	Clinical study report
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
FSH	Follicle-stimulating hormone level
GCP	Good Clinical Practice
GI	Gastrointestinal
H+	Hydrogen
HD	Hemodialysis
IB	Investigational Brochure
IBS	Irritable bowel syndrome
IBS-C	Constipation-predominant irritable bowel syndrome
IBS-D	Diarrhea-predominant irritable bowel syndrome
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine device
min	Minimum (e.g., min, max)
n	Number of observed patients
N	Number of patients in the applicable analysis set
Na+	Sodium

Abbreviation	Definition
NHE3	Na/hydrogen antiporter 3
p	Probability; p-value
PD	Peritoneal dialysis
PK	Pharmacokinetic
PTH	Parathyroid hormone
QD	quaque die, once per day
RBC	Red blood cell
s	serum
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SOP	Standard operating procedure
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 phosphorus 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. Experimental studies provide support for the epidemiologic findings: phosphorus 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 phosphorus 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 phosphorus-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 phosphorus absorption, predominantly through reduction of passive paracellular phosphorus influx, the most important overall mechanism of intestinal phosphorus absorption. Tenapanor modulates tight junctions to increase TEER, thereby reducing paracellular phosphorus permeability; this effect is mediated exclusively via on-target NHE3 inhibition.

Tenapanor has been administered to approximately 400 healthy subjects at single doses up to 900 mg, and in repeated doses up to 180 mg/day for 7 days, and to approximately 1350 IBS-C patients at doses up to 100 mg/day for up to one year and to >900 CKD patients (CKD stages 3b, 4 and 5D) for up to one year 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 Phosphate Binder

The phosphate binder 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.

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 phosphorus-lowering agents and improved dosing with reduced pill burden, which merits further clinical development.

A nonclinical study in Sprague-Dawley rats demonstrated that the administration of tenapanor in combination with sevelamer produced a synergistic effect on the excretion of phosphorus in the feces and therefore had a greater effect in inhibhiting the absorption of dietary phosphorus than either drug alone. Based on this data and the inability of phosphate binders alone to get a majority of patients' serum phosphorus below 4.6 mg/dL, this study is designed to investigate the long term potential of the combination of tenapanor and sevelamer to normalize ESRD patient's serum phosphorus levels.

2.5 Risk-Benefit Assessment

This risk-benefit assessment is based on the nonclinical toxicology, safety, and pharmacology studies as well as the 21 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 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 phosphorus 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 phosphorus 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 Investigator's 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 18 month 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 objective of this study is:

- To evaluate the ability of tenapanor alone or in combination with sevelamer to achieve serum phosphorus concentration (sP) within the population reference range (sP $\geq$2.5 and $\leq$4.5 mg/dL) in patients with end-stage renal disease on dialysis with hyperphosphatemia (>4.5 mg/dL).

3.2 Secondary Objectives

The secondary objectives of this study are:

- To compare the phosphorus lowering effect of tenapanor and sevelamer alone in patients with sP >4.5 mg/dL to patients treated with a combination of tenapanor and sevelamer.
- To evaluate the effect of tenapanor alone and in combination with sevelamer on the proportion of patients reaching serum phosphorus targets defined as ≤4.5 mg/dL.
- To evaluate the effect of the addition of tenapanor to patients taking sevelamer on the percentage reduction in the sevelamer dose.
- To evaluate the effect of tenapanor alone and in combination with sevelamer on intact fibroblast growth factor 23 (iFGF23).
- To evaluate the effect of tenapanor alone and in combination with sevelamer on the Kidney Disease Quality of Life (KDQoL) survey.
- To evaluate the effect of tenapanor alone and in combination with sevelamer on the Dialysis Symptom Index (DSI) survey (for English speakers only).
- To compare the long-term safety of tenapanor alone and in combination with sevelamer.

3.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate the effect of tenapanor alone and in combination with sevelamer on PTH, CRP, aldosterone and other cardio-renal biomarkers (These data may not be part of the study report.)
- To collect and store plasma/serum for future exploratory research into serum/plasma biomarkers related to cardio-renal disease and/or mineral metabolism or that may influence the response (i.e. distribution, metabolism, safety, tolerability, and efficacy) to tenapanor. (These data will not be part of the study report.).

4 STUDY DESIGN

4.1 Design Summary

Patients who complete the TEN-02-301 study (PHREEDOM) at Visit 23, may be eligible to enroll into TEN-02-401 (NORMALIZE).

Patients will be required to sign an ICF and meet all inclusion and no exclusion criteria. No baseline assessments will be performed as part of this protocol; all baseline data for TEN-02-401 will be taken from the TEN-02-301 End of Treatment (EOT) visit. Patients from the

TEN-02-301 tenapanor arm will either receive only tenapanor or be given sevelamer in addition to tenapanor based on their sP following a protocol-specified dose titration schedule. Patients from the TEN-02-301 sevelamer arm will be given tenapanor in addition to their sevelamer dose and the sevelamer dose will then be adjusted based on their sP following a protocol-specified dose titration schedule. Patients will be monitored for safety and efficacy with in-office and telephone visits for up to an additional 18 months.

All study visits 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 and blood collections for laboratory assessments **must** be performed pre-dialysis. All other assessments may be performed pre-, during, or post-dialysis but should be performed at the same time at each visit. For patients receiving PD, visits should be performed on the same day each week, if possible.

Investigators may decrease or increase the dose of tenapanor based on sP 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. The dose of sevelamer carbonate may be adjusted based on the guidance provided in Section 4.1.1 or the sevelamer package insert. Investigators have flexibility to dose sevelamer, TID, BID or QD based on their experience with each patient or as per package insert.

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

Safety assessments will be performed during the study and will include physical examination, vital signs (blood pressure and pulse), body weights, clinical laboratory tests, 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. pharmacokinetics, metabolism, 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

Patients who complete the TEN-02-301 study and enroll into TEN-02-401 study will enter the study from either the tenapanor arm or the sevelamer arm.

Tenapanor Arm

The dosing regimens described below for sevelamer are for guidance to the Investigators. Investigators have flexibility to dose sevelamer, TID, BID or QD based on their experience with each patient or as per package insert. Dosing regimens can be adjusted based on the most recent sP laboratory data (central laboratory data or standard of care local laboratory data).

If patients are in the tenapanor arm (from the TEN-02-301 study), sevelamer will be added as described below:

- sP ≥2.5 and ≤4.5 mg/dL: no addition of sevelamer.
- sP >4.5 and ≤5.0 mg/dL: add one 800 mg tablet QD.
- sP >5.0 and ≤5.5 mg/dL: add one 800 mg tablet BID.
- sP >5.5 mg/dL: add one 800 mg tablet TID.

If sP is still greater than or becomes >4.5 mg/dL at a subsequent visit, sevelamer dose can be increased in a stepwise manner as described below:

- sP >4.5 and ≤5.0 mg/dL: add one 800 mg tablet to the existing regimen.
- sP >5.0 and ≤5.5 mg/dL: add two 800 mg tablets to the existing regimen.
- sP >5.5 mg/dL: add three 800 mg tablets each day (800 mg TID) to the existing regimen.

The maximum dose of sevelamer should be based on standard of care, the sevelamer package insert, and the Investigator's experience with each patient.

If sP <2.5 mg/dL at any visit

- Sevelamer dose can be lowered by one 800 mg tablet TID, or as appropriate, based on current regimen; Investigators have flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert.
- If patient is not taking sevelamer then tenapanor dose can be lowered by one 10 mg tablet BID, unless already at tenapanor 10 mg BID, then can dose tenapanor 10 mg QD

Sevelamer Arm

If patients are from the TEN-02-301 sevelamer arm, tenapanor dose will be added based on their baseline sP as described below. Investigators may decrease or increase the tenapanor dose based on sP levels and/or GI tolerability in 10 mg increments to a minimum of 10 mg QD or a maximum of 30 mg BID, not more than once daily. Dosing regimens can be adjusted based on the most recent sP laboratory data (central laboratory data or standard of care local laboratory data).

- sP >2.5 and ≤3.5 mg/dL: add three 10 mg tablets of tenapanor QD and Sevelamer dose can be lowered by one 800 mg tablet TID.
- sP >3.5 and ≤4.5 mg/dL: add three 10 mg tablets of tenapanor QD
- sP ≥4.5: add three 10 mg tablets of tenapanor BID

If sP >4.5 mg/dL at next visit

- add three 10 mg tenapanor tablets, if on QD regimen to a maximum of 30 mg tenapanor BID. If on 30 mg tenapanor BID follow sevelamer dose regimen changes described below.

Sevelamer dose can be increased by at least one 800 mg tablet at the largest meal and up to one 800 mg tablet TID; Investigators have flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert. If sP <2.5 mg/dL at any visit:

- Sevelamer dose can be lowered by one 800 mg tablet TID; Investigators have flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert.
- If patient is not taking sevelamer then tenapanor dose can be lowered by one 10 mg tablet BID, unless already at tenapanor 10 mg BID, then can dose tenapanor 10 mg QD

4.1.2 Duration of Study

The expected duration of each patient's participation in the study will be up to 18 months.

5 SELECTION AND WITHDRAWAL OF PATIENTS

Investigator(s) will record 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. Completion of TEN-02-301 (Visit 23).
3. Women 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 (from TEN-02-301 study), or 60 years of age or greater..
    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.
    d. Male partner who is sterile or using a condom with spermicide.
4. Male participants 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 30 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. 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. 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.

2. Life expectancy <12 months.
3. 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 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.

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 13 (EOT) will be completed, if possible.

5.4 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.

6 TREATMENT OF PATIENTS

6.1 Administration of Investigational Product

6.1.1 Identity of Investigational Product(s)

6.1.1.1 Tenapanor

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

6.1.1.2 Sevelamer

Sevelamer carbonate will be supplied, as commercially available. [redacted].

6.1.2 Treatments Administered

Tablets containing 10 mg of tenapanor will be taken once or twice daily PO just prior to breakfast and dinner (for QD biggest meal of the day). 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 between 10mg and 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.

Sevelamer should be taken as described in the protocol or in the package insert.

6.1.3 Dose Adjustments

All patients in the tenapanor group will start at the dose that they were receiving at the end of the TEN-02-301 study. Dosing regimens can be adjusted based on the most recent sP laboratory data (central laboratory data or standard of care local laboratory data).

Tenapanor Arm

The dosing regimens described below for sevelamer are for guidance to the Investigators. Investigators have flexibility to dose sevelamer, TID, BID or QD based on their experience with each patient or as per package insert. Dosing regimens can be adjusted based on the most recent sP laboratory data (central laboratory data or standard of care local laboratory data).

If patients are in the tenapanor arm (from the TEN-02-301 study), sevelamer will be added as described below:

- sP ≥2.5 and ≤4.5 mg/dL: no addition of sevelamer.
- sP >4.5 and ≤5.0 mg/dL: add one 800 mg tablet QD.
- sP >5.0 and ≤5.5 mg/dL: add one 800 mg tablet BID.
- sP >5.5 mg/dL: add one 800 mg tablet TID.

If sP is still greater than or becomes >4.5 mg/dL at a subsequent visit, sevelamer dose can be increased in a stepwise manner as described below:

- sP >4.5 and ≤5.0 mg/dL: add one 800 mg tablet to the existing regimen.
- sP >5.0 and ≤5.5 mg/dL: add two 800 mg tablets to the existing regimen.
- sP >5.5 mg/dL: add three 800 mg tablets each day (800 mg TID) to the existing regimen.

The maximum dose of sevelamer should be based on standard of care, the sevelamer package insert, and the Investigator's experience with each patient.

If sP <2.5 mg/dL at any visit

- Sevelamer dose can be lowered by one 800 mg tablet TID, or as appropriate, based on current regimen; Investigators have flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert.
- If patient is not taking sevelamer then tenapanor dose can be lowered by one 10 mg tablet BID, unless already at tenapanor 10 mg BID, then can dose tenapanor 10 mg QD

Sevelamer Arm

If patients are from the TEN-02-301 sevelamer arm, tenapanor dose will be added based on their baseline sP as described below. Investigators may decrease or increase the tenapanor dose based on sP levels and/or GI tolerability in 10 mg increments to a minimum of 10 mg QD or a maximum of 30 mg BID, not more than once daily. Dosing regimens can be adjusted based on the most recent sP laboratory data (central laboratory data or standard of care local laboratory data).

- sP >2.5 and ≤3.5 mg/dL: add three 10 mg tablets of tenapanor QD and Sevelamer dose can be lowered by one 800 mg tablet TID.
- sP >3.5 and ≤4.5 mg/dL: add three 10 mg tablets of tenapanor QD
- sP ≥4.5: add three 10 mg tablets of tenapanor BID

If sP >4.5 mg/dL at next visit

- add three 10 mg tenapanor tablets, if on QD regimen to a maximum of 30 mg tenapanor BID. If on 30 mg tenapanor BID follow sevelamer dose regimen changes described below

Sevelamer dose can be increased by at least one 800 mg tablet at the largest meal and up to one 800 mg tablet TID; Investigators have flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert. If sP <2.5 mg/dL at any visit:

- Sevelamer dose can be lowered by one 800 mg tablet TID; Investigators have flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert.
- If patient is not taking sevelamer then tenapanor dose can be lowered by one 10 mg tablet BID, unless already at tenapanor 10 mg BID, then can dose tenapanor 10 mg QD.

6.1.3.1 Discontinuation Criteria

See Section 5.3 *Patient Withdrawal*

6.1.4 Method of Assigning Patients to Treatment Groups

Patients will enter the TEN-02-401 study into the same group as from the TEN-02-301 study.

6.2 Investigational Product Storage and Accountability

6.2.1 Storage Conditions

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

Tablets of tenapanor should be stored in the original packaging according to the labeling. Sevelamer 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 shipped by the Sponsor or its representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all study drug. Current dispensing records will also be maintained, including the date, bottle number (for tenapanor), and amount of study drug dispensed, and the patient receiving the drug, to be recorded both on the Master IP log and Subject IP log. All remaining study drug not required by regulations to be held by the clinical facility must be returned to Sponsor or its representative at the last IMV or the COV using the study drug return form provided.

6.3 Packaging and Labeling

6.3.1 Study Drug

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

6.3.2 Blinding Methods

The study is open labeled and study drug will not be blinded.

6.4 Concomitant Medications

6.4.1 Concomitant Therapy

The use of concomitant medications during the study, will only be recorded in this study if it is a major change from the medications used at entry into the TEN-02-401 study.

A major change is defined as the addition of a new drug used to treat a serious adverse event (SAE) or the removal of a drug due to the improvement of a disease/condition (i.e., blood pressure improvement)

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

No baseline assessments will be performed as part of this protocol; all baseline data for TEN-02-401 will be taken from the TEN-02-301 End of Treatment (EOT) visit, if available, and include the following:

- Date of birth, gender, and race
- Weight (pre-dialysis) and height (kg and cm, respectively)
- Kt/V – most recent value prior to enrolling into TEN-02-401

- KDQoL survey
- DSI survey (for English speakers only)
- Medical history (major medical conditions taken from TEN-02-301)
- Physical examination
- Vital signs (pre-dialysis)
- Electrocardiogram (ECG) evaluation
- Blood sample for clinical laboratory tests
- Pregnancy test, if applicable
- Blood sample for FGF23 and exploratory biomarkers
- Concomitant medications

7.2.1 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.

7.2.2 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.

7.2.3 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.

7.2.4 Electrocardiograms

A 12-lead electrocardiogram (ECG) will be performed in the sitting or supine position (for at least 5 minutes).

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 and PI's conclusion on ECG profile.

The Investigator will assess whether the ECG is normal or abnormal; abnormal will be further subdivided into 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.

7.2.5 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 the study, specified in the Schedule of Events (Section 1.3) will include a pregnancy test, if applicable.

7.2.6 Analysis of Clinical Laboratory Tests

A certified laboratory will be used to process and provide results for the clinical laboratory tests.

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]	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[f] Potassium Sodium	Prothrombin time Activated partial thromboplastin time	Serum pregnancy[g] FGF-23[ch] Parathyroid Hormone (PTH)[e] c-reactive protein[e] Aldosterone[e]

[a] Whole blood.
[b] Serum.
[c] Plasma.
[d] Only in people treated with Warfarin.
[e] May be performed from the biomarker samples, if desired and will not be part of the clinical study report.
[f] Serum phosphorus is also performed separately from standard clinical laboratory tests at protocol specified time points.
[g] Serum pregnancy tests will only be performed on women of child-bearing potential.
[h] Intact FGF-23 will be measured.

7.2.7 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 enrollment visit through the end of treatment (Visit 13). 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 13 (EOT) 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 7.2.7.8 are to be followed for reporting SAEs.

7.2.7.1 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."

7.2.7.2 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.

7.2.7.3 Assessment of Adverse Events

The relationship of the event to the study drug 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, or the temporal relationship of the event to study drug administration makes a causal relationship unlikely
- Possibly related: The event follows a reasonable temporal sequence from the time of drug administration, and 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, and cannot be reasonably explained by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs.

7.2.7.4 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.

7.2.7.5 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.

7.2.7.6 Pregnancy

Female patients must be instructed to discontinue tenapanor 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 tenapanor. 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 tenapanor until 30 days after last exposure.

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].

7.2.7.7 Serious Adverse Events

An SAE is any AE occurring from Enrollment through final study visit (V13), 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.

7.2.7.8 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] 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.

Follow-Up Reports

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] 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.

7.3 Efficacy Variables

The following are the efficacy variables for this study:

- Patients reaching serum phosphorus goal levels defined as sP>2.5 and ≤4.5 mg/dL
- Patients reaching serum phosphorus goal levels defined as sP ≤4.5 mg/dL
- Percent change from baseline in sevelamer dose
- Change from baseline in iFGF23 (intact)
- Change from baseline in Kidney Disease and Quality of Life survey (KDQoL) composite score and subscales
    - Kidney Disease and Quality of Life™ (KDQOL™-36) (Copyright© 2000 by RAND and the University of Arizona)
- Change from baseline in Dialysis Symptom Index survey (DSI) overall symptom burden score and overall symptom severity score
    - The University of Pittsburgh Medical Center, VA Pittsburgh Healthcare System (Weisbord et al. J Pain Symptom Manage, 2004:27, 226-40.)

7.4 Exploratory Variables

Plasma and serum samples will be collected at specified times and may be used to evaluate the effect of tenapanor alone and in combination with sevelamer on PTH, CRP, aldosterone and other cardio-renal biomarkers (These data may not be part of the study report.)

Future exploratory research on serum/plasma biomarkers may be performed related to cardio-renal disease and/or mineral metabolism or that may influence the response (i.e. distribution, metabolism, safety, tolerability, and efficacy) to tenapanor. (These data will not be part of the study report.).

8 METHODOLOGY/STUDY VISITS

8.1 Baseline, Visit 1

Prior to enrollment, 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.

No baseline assessments will be performed as part of this protocol; all baseline data for TEN-02-401 will be taken from the TEN-02-301 End of Treatment (EOT) visit and will consist of the following:

- Informed consent
- Inclusion and exclusion criteria (Section 5)
- Weight (pre-dialysis)
- Kt/V (most recent measurement prior to enrolling into TEN-02-401)
- Medical history (major medical conditions taken from TEN-02-301)
- Phosphate binder used and dose
- KDQoL survey
- DSI survey (for English speakers only)
- Physical examination (Section 7.2.2)
- Vital signs (pre-dialysis) (Section 7.2.3)
- ECG evaluation (Section 7.2.4)
- Clinical laboratory tests (pre-dialysis) (Section 7.2.5)
    - Serum chemistry
    - Hematology
    - Coagulation profile (if applicable)
- Serum pregnancy test, if applicable
- FGF-23, and exploratory biomarker sample (pre-dialysis)
- Dispense study drug

- Begin collecting adverse events
- Review concurrent medications

8.2 Weeks 1, 2, 3, 4, 6, and 8, Visits 2, 3, 4, 5, 6, and 7

- Serum phosphorus (pre-dialysis)
- Return/accountability of study drug
- Dispense study drug
- Adverse event reporting
- Review concurrent medications

8.3 Months 3, 6, 9, 12, and 15, Visits 8, 9, 10, 11, and 12

- Weight (pre-dialysis)
- Kt/V (most recent measurement prior to screening)
- KDQoL survey (not Months 9 and 15, Visits 10 and 12)
- DSI survey, for English speakers only (not Months 9 and 15, Visits 10 and 12)
- Vital signs (pre-dialysis) (Section 7.2.3)
- Clinical laboratory tests (pre-dialysis) (Section 7.2.5)
  - Serum chemistry
  - Hematology
  - Coagulation profile (if applicable)
- FGF-23, and exploratory biomarker sample (pre-dialysis)
- Return/accountability of study drug
- Dispense study drug
- Adverse event reporting
- Review concurrent medications

8.4 Months 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, Telephone Visit T1, T2, T3, T4, T5, T6, T7, T8, T9, T10

- Adverse event reporting
- Review concurrent medications

8.5 Month 18, Visit 13; End of Treatment Visit

- Weight (pre-dialysis)
- Kt/V (most recent measurement prior to screening)
- KDQoL survey
- DSI survey (for English speakers only)
- Physical examination (Section 7.2.2)
- Vital signs (pre-dialysis) (Section 7.2.3)
- ECG evaluation (Section 7.2.4)
- Clinical laboratory tests (pre-dialysis) (Section 7.2.5)
  - Serum chemistry
  - Hematology
  - Coagulation profile (if applicable)
- Serum pregnancy test, if applicable
- FGF-23, and exploratory biomarker sample (pre-dialysis)
- Return/accountability of study drug
- Adverse event reporting
- Review concurrent medications

8.6 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.

8.7 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 (Visit 13). 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 5.3.

8.8 Total Blood Volume Required for Study

Table 8-1: Approximate Blood Volume per Completed Patient

Test	No. of Samples	Volume (mL)	Total (mL)
Hematology (blood)	7	3	21
Chemistry (serum) (includes serum pregnancy test)	7	7	49
Phosphorus (serum)[#]	6	5	30
iFGF-23 (plasma)	7	4	28
Exploratory biomarker sample (serum and plasma)	7	13	91
Coagulation (plasma)	7	3	21
Total Volume	**--**	**--**	**240**

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

8.9 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 require 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) will be provided separately. 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 150-200 patients with ESRD on hemodialysis (HD) or peritoneal dialysis (PD) will be enrolled in this study. The sample size of this study is not planned based on statistical considerations.

9.3 Analysis Sets

Two analysis sets are defined for this study: Safety Analysis Set and Full Analysis Set (FAS).

Safety Analysis Set:

All patients who receive at least one dose of study drug (tenapanor or sevelamer) in the study. The safety analysis set will be used for the analysis of safety variables.

Full Analysis Set:

All patients who meet the study entry inclusion/exclusion criteria, receive at least one dose of study drug (tenapanor or sevelamer), and have at least one post-baseline sP assessment in TEN-02-401. The FAS will be used for the analysis of efficacy variables.

9.4 Statistical Methods

9.4.1 General Approach

Unless specified otherwise, 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.

9.4.2 Baseline Descriptive Statistics

Baseline characteristics, including demographics, disease characteristics, prior/concomitant medications, and medical/surgical history will be summarized by TEN-02-301 treatment arm and overall for each analysis set.

9.4.3 Efficacy Analysis

All efficacy variables will be descriptively summarized at each visit for the FAS and each TEN-02-301 treatment arm (tenapanor or sevelamer). Descriptive summaries of sP variables will also be repeated for FAS subjects with a baseline sP >4.5 mg/dL.

For response endpoints, the response rate at each post-baseline visit will be estimated with asymptotic 95% confidence interval (CI) for each TEN-02-301 treatment arm. Inferential analyses of sP endpoints will be performed for comparisons of phosphorus-lowering effect between monotherapy (tenapanor and sevelamer alone) and combination therapy (tenapanor combined with sevelamer) unless the sample size in each monotherapy treatment group is less than 15. Detailed model specifications will be provided in the statistical analysis plan (SAP). Inferential analyses of other endpoints may be performed as suggested by the data.

Analyses will be detailed in the statistical analysis plan (SAP).

9.4.4 Procedures for Handling Missing Serum Phosphorus Data

Descriptive summaries of efficacy and safety measures will be based on observed data. No imputation of missing data will be implemented.

Handling of missing data for each inferential analysis will be detailed in the SAP.

9.4.5 Methods of Pooling Data

For the purpose of adjusting for investigator effects in statistical models, investigator sites may 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.

9.4.6 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 are the last data collected during each study period.

9.4.7 Safety Analyses

Safety analyses include summaries for adverse events, clinical laboratory tests, vital signs, body weights, 12-lead ECGs, and physical examinations. These summaries will be provided for the Safety Analysis Set and each TEN-02-301 treatment arm (tenapanor or sevelamer).

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 treatment-emergent adverse events (TEAEs). Actual values and change from baseline values for clinical laboratory tests, vital signs, body weights, and ECGs will be descriptively summarized by visit. The number and percentage of patients in each physical examination category will be presented by 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 applicable 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, 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.

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 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 distributed to all sites. 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, or there is a change in site location, 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

DOPPS 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

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.

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

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.

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.

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.

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.

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