CLINICAL TRIAL PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Tenapanor as Adjunctive Therapy to Phosphate Binder Therapy in End-Stage Renal Disease (ESRD) Subjects with Hyperphosphatemia

Protocol Number: TEN-02-202

22 January 2019

NCT03824587

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Study TEN-02-202

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Protocol Number: TEN-02-202

Edition No. 2:

22 January 2019

Sponsor:
Ardelyx, Inc.
[redacted]

TABLE OF CONTENTS

In-text Figures

In-text Tables

1 GENERAL INFORMATION

1.1 Study Administrative Structure

A randomized, double-blind, placebo-controlled study to evaluate the efficacy of tenapanor as adjunctive therapy to phosphate binder therapy in end-stage renal disease (ESRD) subjects with hyperphosphatemia.

Protocol No.:	TEN-02-202
Sponsor:	Ardelyx, Inc.
Sponsor's Contact:	[redacted]
Medical Monitor:	[redacted]
Clinical Research Organization:	[redacted]

1.2 Synopsis

Protocol Title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy of tenapanor as adjunctive therapy to phosphate binder therapy in end-stage renal disease (ESRD) subjects with hyperphosphatemia

Sponsor: Ardelyx, Inc.

Study Phase: Phase 2/3

Objectives: The primary objective of this study is:

- To evaluate the effect of tenapanor on change in serum phosphorus (s-P) levels when tenapanor is administered orally, twice daily for 28 days as adjunctive therapy to ESRD subjects with hyperphosphatemia on stable phosphate binder therapy.

The secondary objectives of this study are:

- To evaluate the effect of tenapanor versus placebo as adjunctive therapy with phosphate binder to lower subject's s-P level to <5.5 mg/dL.
- To evaluate the effect of tenapanor versus placebo as adjunctive therapy with phosphate binder on intact fibroblast growth factor 23 (iFGF23) and c-terminal fibroblast growth factor 23 (cFGF23).
- To evaluate the effect of tenapanor versus placebo as adjunctive therapy with phosphate binder on parathyroid hormone (PTH).

The exploratory objective of this study is:

- To collect and store plasma/serum for future exploratory research into serum/plasma biomarkers related to cardiorenal 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 clinical study report.

Number of Sites: 40 to 50

Study Design: This is a randomized, double-blind, placebo-controlled study to evaluate the effect of tenapanor on change in s-P levels when tenapanor is administered orally, twice daily for 28 days as adjunctive therapy to ESRD subjects with hyperphosphatemia on stable phosphate binder therapy.

The study consists of a Screening visit; a Run-in Period of at least 2 weeks and up to 4 weeks, where existing phosphate binder treatment is maintained; and a 4-week Double-Blind Treatment Period, during which subjects are randomized in a 1:1 ratio to receive tenapanor or placebo treatment while continuing their existing phosphate binder treatment. The dose of phosphate binder should remain unchanged throughout the study (from Screening to the end of study)

The Screening visit (Visit 1) and all other visits in the study must be scheduled after a short dialysis interval (Wednesday or Friday for subjects on a Monday-Wednesday-Friday schedule and Thursday or Saturday for

subjects on a Tuesday-Thursday-Saturday schedule). Body weight, vital signs, 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.

At Screening (Visit 1), a subject must be on thrice daily phosphate binder therapy and have a s-P level ≥5.5 and ≤10.0 mg/dL to qualify for entering the study. The subject should be told to continue their existing phosphate binder treatment throughout the study without any change to the phosphate binder dose. Serum phosphorus will be measured at each visit (pre-dialysis after a short interval) during the Run-in Period to enable the evaluation of the s-P randomization criteria. To be randomized at Visit 4 (Day 1), subjects must have a s-P level ≥5.5 and ≤10.0 mg/dL at Visit 3.

Subjects who do not meet the randomization criteria based on the s-P level at Visit 3 will be discontinued as screen failures. Subjects must continue to meet all other applicable inclusion/exclusion criteria at randomization. Those subjects who meet the s-P criteria at Screening (Visit 1), but screen fail due to the s-P level at Visit 3 can be re-screened; they must wait a minimum of one week after screen failing to be re-screened.

During the Double-Blind Treatment Period, subjects will receive tenapanor or placebo starting at a dose of 30 mg twice daily (bid; three 10 mg tablets each time). Tenapanor or placebo will be taken twice daily; just prior to breakfast and dinner. Subjects should **not** take study medication at the meal immediately preceding dialysis.

Investigators may decrease or increase the dose of study medication based on s-P levels and/or gastrointestinal (GI) tolerability in 10 mg increments to a minimum of 10 mg bid or a maximum of 30 mg bid after Randomization (Visit 4) to Day 15 (Visit 6). Doses can be adjusted between visits.

Safety assessments will be performed at various time points throughout the study and will include physical examination, body weight, vital signs, safety laboratory tests, 12-lead electrocardiogram (ECG), and adverse event (AE) recording.

Blood samples will be collected and stored, as appropriate, for the potential evaluation of exploratory biomarkers.

Planned Sample Size: Approximately 214 ESRD subjects will be randomized in this study.

Subject Selection Criteria:

Inclusion Criteria:

1. Signed and dated informed consent prior to any study specific procedures.
2. Males or females aged 18 to 80 years, inclusive, at Screening (Visit 1).
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: intrauterine device (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 from Screening (Visit 1) until 30 days after the last subject visit.

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 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. Chronic maintenance hemodialysis (HD) 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, the subject must meet one of the two dialysis criteria above and been on the new modality of dialysis for a minimum of one month.

6. If receiving active vitamin D or calcimimetics, the dose should have been unchanged for the last 4 weeks prior to Screening (Visit 1).

7. Kt/V $\geq$1.2 at most recent measurement prior to Screening (Visit 1).

8. Prescribed and taking phosphate binder medication at least 3 times per day. The prescribed dose should have been unchanged during the last 4 weeks prior to Screening (Visit 1).

9. Serum phosphorus levels must be $\geq$5.5 and $\leq$10.0 mg/dL at Screening (Visit 1) and the end of the Run-in Period (Visit 3), analyzed at the central laboratory used in the study.

10. Able to understand and comply with the protocol.

Exclusion Criteria:

1. Severe hyperphosphatemia defined as having an s-P level >10.0 mg/dL on phosphate-binders at any time point during routine clinical monitoring for the 3 preceding months before Screening (Visit 1).
2. Serum/plasma parathyroid hormone >1200 pg/mL. The most recent value from the subject's medical records should be used.
3. Clinical signs of hypovolemia at Screening (Visit 1) as judged by the Investigator.
4. History of inflammatory bowel disease (IBD) or irritable bowel syndrome with diarrhea (IBS-D).
5. Scheduled for living donor kidney transplant or plans to relocate to another center during the study period.
6. Use of an investigational agent within 30 days prior to Screening (Visit 1).
7. Involvement in the planning and/or conduct of the study (applies to both Ardelyx/Contract Research Organization (CRO) staff and/or staff at the study site).
8. If, in the opinion of the Investigator, the subject is unable or unwilling to fulfill the requirements of the protocol or has a condition which would render the results uninterpretable.

Study Medication: Tenapanor 10 mg tablets or matched placebo tablets

Safety and Efficacy Measures:

Safety Measures:

Physical examination; body weight; vital signs; 12-lead ECG; safety laboratory tests (routine serum chemistry and hematology); and AE monitoring.

Efficacy Measures:

Serum phosphorus, iFGF23, cFGF23, and PTH.

Statistical Analyses:

Analysis Populations:

- **Intent-to-Treat (ITT) Population:** will be comprised of all randomized subjects.
- **Full Analysis Set (FAS):** will include all ITT subjects who have at least one post-baseline s-P measurement during the study. It will be the population used for efficacy analyses to be performed with subjects as randomized.
- **Per-Protocol Population:** will be a subset of the FAS. It will be the analysis population for sensitivity analysis to be performed with subjects as randomized. Any subject who has a significant protocol deviation that could alter his/her efficacy outcome to treatment will be excluded from the PP population.

- **Week 4 Completers:** will be a subset of the FAS. It will include all FAS subjects who complete the s-P assessment at Week 4. It will be the analysis population for sensitivity analysis to be performed with subjects as randomized.
- **Safety Population:** will include all ITT subjects who receive at least one dose of study medication (tenapanor or placebo). It will be the analysis population for safety analyses to be performed with subjects as treated.

Safety Analyses:

All safety measures will be summarized descriptively. AEs will be summarized by MedDRA system organ class and preferred term.

Efficacy Analyses:

The primary efficacy endpoint is the change from baseline in s-P level at Week 4. For this continuous endpoint, the following pair of hypotheses will be tested:

$$H_0: \mu_t = \mu_p$$

versus

$$H_1: \mu_t \neq \mu_p$$

where μ_t and μ_p denote the mean changes from baseline in s-P level at Week 4 in the tenapanor and placebo groups, respectively. As the primary analysis, the treatment comparison of the mean change will be performed using a mixed-effects model for repeated measures (MMRM) on observed cases of the FAS. The MMRM will include type of phosphate binder (sevelamer or non-sevelamer), s-P level at Visit 3 (<7.5 mg/dL or ≥7.5 mg/dL), treatment, visit (Week 1 through Week 4), treatment-by-visit interaction as fixed effects; baseline (Visit 4) s-P level and baseline-by-visit as covariates; and subject as a random effect. An unstructured covariance matrix will be used to model the within-subject errors.

The MMRM approach will also be applied to the analysis of changes from baseline in s-P at Week 1, Week 2, and Week 3. An analysis of variance (or covariance) will be performed for iFGF23/cFGF23 (or PTH) endpoints.

For binary response endpoints, the response rate defined as the proportion of subjects reaching an s-P level <5.5 mg/dl will be estimated at each post-baseline visit and compared between treatment groups.

1.3 Schedule of Assessments and Procedures

	Screening	Run-in Period		Treatment Period				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8/ET
	Week -4 to -3	Week -2	Week -1	Day 1	Week 1	Week 2	Week 3	Week 4
Visit Window	-30 to -14[d]	-18 to -7 (5-16 days after V1)	-9 to -2 (5-9 days after V2)	1[e] (2-9 days after V3)	8 ± 2	15 ± 2	22 ± 2	29 ± 2
Study Procedure								
Informed Consent	X							
Inclusion/ Exclusion Criteria	X			X[f]				
Demographics	X							
Medical/Surgical History	X			X[g]				
Prior/Con Meds	X	X	X	X	X	X	X	X
Physical Examination	X							X
Weight (pre-dialysis)	X							X
Height	X							
Vital Signs[a]	X			X				X
12-lead ECG	X							X
Safety Laboratory Evaluations[b]	X							X
Serum Phosphorus	X	X*	X	X	X	X	X	X
FSH Test[c]	X							
Pregnancy Test[c]	X							X
Randomization				X				
Study Medication Dispense and/or Return				X	X	X	X	X
FGF23 and PTH Blood Sample				X				X
Biomarker Blood Sample				X				X
AE Assessment		X	X	X	X	X	X	X

* At Visit 2, a serum phosphorus level of <5.5 mg/dL or >10.0 mg/dL does not deem the subject ineligible. However, the subject may be discontinued at the Investigator's discretion.

[a] Vital signs include sitting or supine blood pressure and pulse, prior to dialysis.

[b] Safety laboratory evaluations will include the hematology and serum chemistry tests other than the serum phosphorus test listed in Table 7-1.

[c] FSH (postmenopausal females) and pregnancy tests are performed on all females <60 years of age unless there is a documented method of sterilization, or FSH test confirms post-menopausal status.

[d] Screening (Visit 1) could be 14 to 30 days (i.e. 2 to 4 weeks) before randomization following the short-interval schedule.

[e] Day 1 is the randomization day and serves as the reference day for all visits.

[f] Subjects must continue to meet all applicable inclusion/exclusion criteria before randomization, including the criteria based on the s-P level at Visit 3.

[g] Record only changes to medical history from Visit 1

1.4 List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransaminase
bid (b.i.d.)	bis en die, twice a day
BUN	blood urea nitrogen
cFGF23	c-terminal fibroblast growth factor 23
CFR	Code of Federal Regulations (United States)
CI	confidence interval
CKD	chronic kidney disease
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ESRD	end-stage renal disease
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HD	hemodialysis
HDPE	high-density polyethylene
IB	Investigator's Brochure
IBD	irritable bowel disease
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhea
ICF	informed consent form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
iFGF23	intact fibroblast growth factor 23

Abbreviation	Definition
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
IUD	intrauterine device
Kt/V	a measure of dialysis adequacy
LOCF	last-observation-carried-forward
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	mixed-effects for repeated measures
NHE3	sodium-hydrogen exchanger 3
PD	peritoneal dialysis
PP	Per-Protocol
PTH	parathyroid hormone
p-value	probability value
QRS	principal deflection in ECG
QT	ECG interval
QTc	QT interval which has been corrected by taking into account heart rate
RBC	red blood cell
RR	ECG interval between two consecutive R waves
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
s-P	serum phosphorus
TEAE	treatment-emergent adverse event
tid (or t.i.d.)	ter in die, three times a day
UN	unstructured
WBC	white blood cell count

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 2005). 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 19 July 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 (s-P) 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 large proportion of ESRD patients still do not achieve adequate phosphorus control (DOPPS Practice Monitor 2018). 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 gastrointestinal (GI) 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 medications with new mechanisms of action, a more convenient dosing, and improved risk-benefit profile.

Tenapanor is an oral, minimally absorbed compound that inhibits the sodium-hydrogen exchanger 3 (NHE3) transporter locally in the GI 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 the transepithelial electrical resistance, 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; to approximately 1020 subjects with irritable bowel syndrome with constipation (IBS-C), at doses up to 100 mg/day for up to 12 weeks; and to 477 CKD subjects (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 $C_{50}H_{68}Cl_6N_8O_{10}S_2$.

Tenapanor tablets will be supplied as yellow, oval biconvex film-coated tablets [redacted]

Dosing consists of one to three 10 mg tablets, taken twice daily just prior to breakfast and dinner (but not prior to the meal immediately prior to dialysis).

Tenapanor tablets (10 mg, administered as 10.6 mg of the hydrochloride salt) are packaged in an opaque white high-density polyethylene (HDPE) bottle (60/bottle) with a white polypropylene child resistant closure and induction seal plus a desiccant canister. Tablets of tenapanor should be stored in the original packaging according to the labeling.

2.3 Study Rationale

Tenapanor is an investigational product being evaluated for its ability to lower s-P levels in CKD subjects on dialysis with hyperphosphatemia. Most ESRD subjects currently take phosphate binders to control s-P levels. A significant proportion of ESRD patients still do not achieve adequate phosphate control (DOPPS Practice Monitor 2018). Since tenapanor lowers s-P levels via a different mechanism of action, it is believed that adjuvant therapy of tenapanor with current phosphate binder therapy will produce additional phosphate-lowering activity. In rats, tenapanor dosed with sevelamer carbonate (a phosphate binder) significantly increased the amount of phosphorus in the feces as compared to administration of sevelamer carbonate alone; the increase in fecal phosphorus is an in vivo pharmacodynamic effect of phosphate lowering therapies.

2.4 Risk-Benefit Assessment

The risk-benefit assessment of tenapanor is based on nonclinical toxicology, safety, and pharmacology studies as well as 19 clinical trials conducted with tenapanor. Results from the risk-benefit assessment are described in the Investigator's Brochure (IB).

Nonclinical toxicological studies of up to 9 months have been conducted 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 medication. 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; to 1020 IBS-C subjects at doses up to 100 mg/day for up to 12 weeks; and to 477 CKD subjects (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 samples) have quantifiable tenapanor present in blood plasma (lower limit of quantification = 0.5 ng/mL); all samples with quantifiable 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 or looser stools and increase stool frequency. Tenapanor has been demonstrated to be generally

safe and well tolerated in clinical studies. The safety profile with softening or loosening of stool consistency and GI adverse events (AEs) have been consistent with its pharmacology.

The theoretical AEs from tenapanor treatment in ESRD subjects would be due to exaggerated pharmacological effects and may include electrolyte disturbances, metabolic acidosis, soft stools/diarrhea, and reduced blood pressure. While a softening or loosening of the stool with an increased fluid loss via the intestine is an intended and desired effect of tenapanor in some subjects, sensitive subjects should be monitored for signs of dehydration in case of prolonged severe diarrhea. This study protocol includes clinical laboratory tests and vital signs. The health status of each study subject will be checked at each visit. All subjects will continue their existing treatment with phosphate binders when their participation in the study ends. See the IB for details on non-clinical and clinical results with tenapanor.

Subjects will be informed both verbally and in writing about these aspects before taking part in any study-specific examination. 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, risks to participants in this short-term study are considered acceptable. Results from this study will be important for the development of a potential new drug, which could improve the treatment of hyperphosphatemia in ESRD subjects.

3 STUDY OBJECTIVES

3.1 Primary Objective

- To evaluate the effect of tenapanor on change in s-P levels when tenapanor is administered orally twice daily for 28 days as adjunctive therapy to ESRD subjects with hyperphosphatemia on stable phosphate binder therapy.

3.2 Secondary Objective

- To evaluate the effect of tenapanor versus placebo as adjunctive therapy with phosphate binder to lower subject's s-P level to <5.5 mg/dL.
- To evaluate the effect of tenapanor versus placebo as adjunctive therapy with phosphate binder on intact fibroblast growth factor 23 (iFGF23) and c-terminal fibroblast growth factor 23 (cFGF23).
- To evaluate the effect of tenapanor versus placebo as adjunctive therapy with phosphate binder on parathyroid hormone (PTH).

3.3 Exploratory Objective

- To collect and store plasma/serum for future exploratory research into serum/plasma biomarkers related to cardiorenal 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 clinical study report.

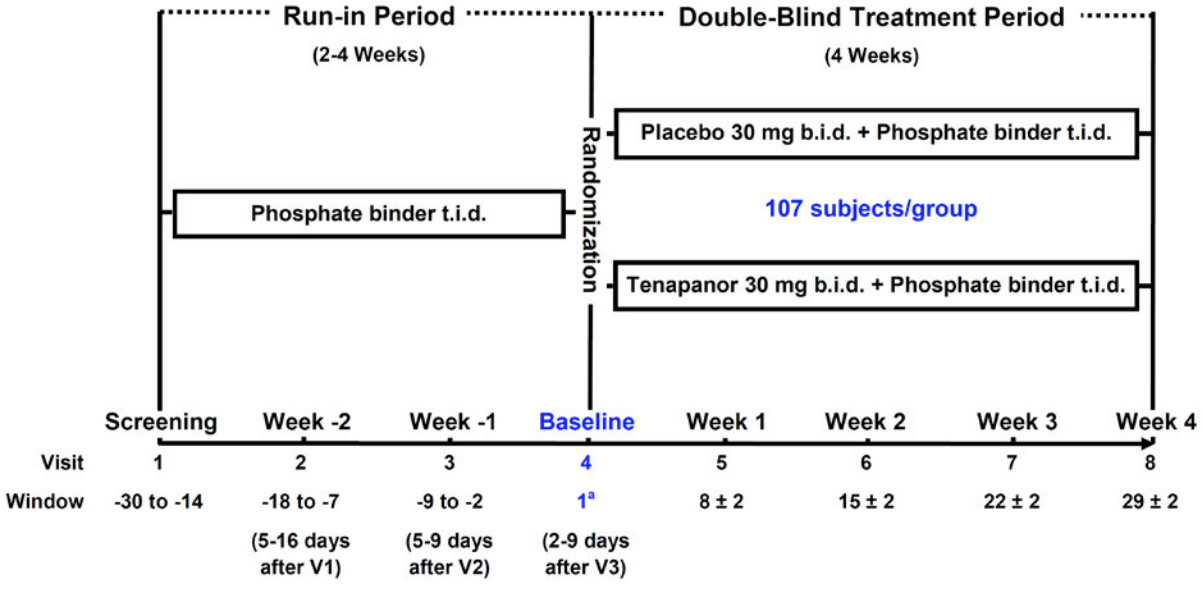
4 STUDY DESIGN

4.1 Design Summary

This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy of tenapanor as adjunctive therapy to phosphate binder therapy in ESRD subjects with hyperphosphatemia.

The study consists of a Screening visit; a Run-in Period of at least 2 weeks and up to 4 weeks, where existing phosphate binder treatment is maintained; and a 4-week Double-Blind Treatment Period, during which subjects are randomized in a 1:1 ratio to receive tenapanor or placebo at a dose of 30 mg twice daily (bid; three 10 mg tablets each time) while continuing their existing phosphate binder treatment. The dose of phosphate binder should remain unchanged throughout the study (from Screening to the end of study). Approximately 214 subjects will be randomized at 40 to 50 sites.

Figure 4-1: Study Design Diagram



[a] Day 1 is the randomization day and serves as the reference day for all visits.

The Screening visit (Visit 1) and all other visits in the study must be scheduled after a short dialysis interval (Wednesday or Friday for subjects on a Monday-Wednesday-Friday schedule and Thursday or Saturday for subjects on a Tuesday-Thursday-Saturday schedule). Body weight, vital signs, 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.

At Screening, a subject must be on thrice daily phosphate binder therapy and have a s-P level ≥5.5 and ≤10.0 mg/dL to qualify for entering the study. The subject should be told to continue their existing phosphate binder treatment throughout the study without any change to the phosphate binder dose. Serum phosphorus will be measured at each visit (pre-dialysis after a short interval) during the Run-in Period to enable evaluation of the s-P randomization criteria. To be randomized at Day 1 (Visit 4), subjects must have a s-P level ≥5.5 and ≤10.0 mg/dL at Visit 3.

Subjects who do not meet the randomization criteria based on the s-P level at Visit 3 will be discontinued as screen failures. Subjects must continue to meet all other eligible inclusion/exclusion criteria at randomization. Subjects who meet the s-P criteria at Screening (Visit 1), but screen fail due to the s-P level at Visit 3 can be re-screened; they must wait a minimum of one week after screen failing to be re-screened.

During the Double-Blind Treatment Period, subjects will receive tenapanor or placebo starting at a dose of 30 mg bid (three 10 mg tablets each time). Tenapanor or placebo will be taken twice daily; just prior to breakfast and dinner. Subjects should **not** take study medication at the meal immediately preceding dialysis.

Investigators may decrease or increase the dose of study medication 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 after Randomization (Visit 4) to Day 15 (Visit 6). Doses can be adjusted between visits.

Safety assessments will be performed at various time points throughout the study and will include physical examination, body weight, vital signs, safety laboratory tests, 12-lead electrocardiogram (ECG), and AE recording.

Blood samples will be collected, processed to serum or plasma, and stored, as appropriate, for the potential evaluation of exploratory biomarkers.

4.1.1 Duration of Study

The treatment duration of this study will be 4 weeks.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

A subject 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 aged 18 to 80 years, inclusive, at Screening (Visit 1).
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: intrauterine device (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 from Screening until 30 days after the last subject visit.
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 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. Chronic maintenance hemodialysis (HD) 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, subject must meet one of the two dialysis criteria above and been on the new modality of dialysis for a minimum of one month.
6. If receiving active vitamin D or calcimimetics, the dose should have been unchanged for the last 4 weeks prior to Screening (Visit 1).
7. Kt/V $\geq$1.2 at most recent measurement prior to Screening (Visit 1).

8. Prescribed and taking phosphate binder medication at least 3 times per day. The prescribed dose should have been unchanged during the last 4 weeks prior to Screening (Visit 1).
9. Serum phosphorus levels must be ≥5.5 and ≤10.0 mg/dL at Screening (Visit 1) and the end of the Run-in Period (Visit 3), analyzed at the central laboratory used in the study.
10. Able to understand and comply with the protocol.

5.2 Exclusion Criteria

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

1. Severe hyperphosphatemia defined as having an s-P level >10.0 mg/dL on phosphate-binders at any time point during routine clinical monitoring for the 3 preceding months before Screening (Visit 1).
2. Serum/plasma parathyroid hormone >1200 pg/mL. The most recent value from the subject's medical records should be used.
3. Clinical signs of hypovolemia at Screening (Visit 1) as judged by the Investigator.
4. History of inflammatory bowel disease (IBD) or irritable bowel syndrome with diarrhea (IBS-D).
5. Scheduled for living donor kidney transplant or plans to relocate to another center during the study period.
6. Use of an investigational agent within 30 days prior to Screening (Visit 1).
7. Involvement in the planning and/or conduct of the study (applies to both Ardelyx/CRO staff and/or staff at the study site).
8. If, in the opinion of the Investigator, the subject is unable or unwilling to fulfill the requirements of the protocol or has a condition which would render the results uninterpretable.

5.3 Subject Withdrawal

Subjects are free to discontinue the study at any time, for any reason, and without prejudice to further treatment. The Investigator may remove a subject if, in the Investigator's judgment, continued participation would pose unacceptable risk to the subject or to the integrity of the study data. If possible, all procedures for early termination will be completed (Section 8.7).

5.4 Early Termination of Study

The study may be terminated at any time by the Sponsor if serious side effects occur, or if, in the Sponsor's judgment, there are no further benefits to be achieved from the study, or for administrative reasons. A site may be closed out if the Investigator does not adhere to the protocol or GCP. In the event that the clinical development of the investigational product is discontinued, the Sponsor shall inform all Investigators/institutions and the Institutional Review Board (IRB) overseeing the trial.

6 TREATMENT OF SUBJECTS

6.1 Administration of Investigational Product

6.1.1 Identity of Investigational Product(s)

Tenapanor hydrochloride is an amorphous, off-white to white powder. Tenapanor tablets will be supplied as yellow, oval, biconvex tablets packaged in HDPE bottles with a desiccant canister. Each bottle contains sixty (60) 10 mg tablets and a desiccant canister. A matching placebo will be identically supplied in HDPE bottles.

6.1.2 Treatments Administered

All subjects will remain on their phosphate binder for the duration of the study. There should be no change to their phosphate binder dose for the duration of the study.

Tablets containing 10 mg of tenapanor or corresponding placebo will be taken orally twice daily just prior to breakfast and dinner. On dialysis days, subjects on HD should not take study medication at the meal immediately prior to dialysis and instead take it just prior to 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.

6.1.3 Dose Adjustments

All subjects will start at a dose of 30 mg bid (three 10 mg tenapanor or placebo tablets each time). After randomization (Visit 4) to Day 15 (Visit 6), doses can be adjusted in 10 mg increments based on s-P 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. Doses can be adjusted between visits.

6.1.4 Method of Assigning Subjects to Treatment Groups

After giving informed consent, subjects will be allocated sequential enrollment numbers at Screening (Visit 1).

A stratified randomization scheme will be employed to this study, with type of phosphate binder (sevelamer or non-sevelamer) and s-P level at Visit 3 (<7.5 mg/dL or ≥7.5 mg/dL) as two stratification factors. The CRO or designated independent statistician will prepare the randomization scheme in accordance with the CRO's standard operating procedures (SOPs) and the randomization plan, which reflect Good Clinical Practice (GCP) standards. Upon completion of the Run-in Period, eligible subjects will be randomized in a 1:1 ratio at Visit 4 (Day 1) to receive tenapanor or placebo.

The randomization of this study will be implemented via an Interactive Response Technology (IRT). The IRT will allocate the treatment and provide the randomization number. The IRT will provide the appropriate bottle ID chosen from those bottle IDs available at the study site for tenapanor and placebo. As the randomization will not be stratified by study site, the assigned randomization numbers and the associated bottle IDs will not be sequential within a study site.

If a subject withdraws from the study, his/her enrollment and randomization numbers cannot be reused.

6.2 Investigational Product Storage and Accountability

6.2.1 Storage Conditions

The Investigator will ensure that all study medications 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.

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 medications shipped by the Sponsor or their representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all study medications. Current

dispensing records will also be maintained including the date and amount of study medications dispensed and the subject receiving study medications. All remaining study medications not required by regulations to be held by the clinical facility must be returned to the Sponsor or their representative immediately after the study completion.

6.3 Packaging and Labeling

6.3.1 Study Medication

Tenapanor tablets (10 mg) are packaged in an opaque white HDPE bottle (60 tablets/bottle) with a white polypropylene child resistant closure and induction seal plus a desiccant canister.

A matching placebo will be identically supplied in HDPE bottles.

Study medications should be stored in the original packaging according to the labeling.

6.3.2 Blinding Methods

Placebo tablets are identical in appearance (shape, color, size, etc.).

Only the party responsible for labeling, warehousing and shipping drug supply; the CRO or designated independent statistician responsible for preparing the randomization list; and the IRT manager responsible for ensuring medication is available at sites will have knowledge of the treatments assigned during the Double-Blind Treatment Period.

6.4 Procedure for Breaking Randomization Code

During the Double-Blind Treatment Period, the blind is to be broken only when the safety of the subject is at risk and knowledge of the study medication is essential to the clinical management of the subject. A decision to unblind a subject must be made in concert with the Medical Monitor and the Sponsor, except in emergency situations when the blind must be broken to determine the treatment for the subject. If a subject is unblinded, the date and reason for the unblinding must be recorded on source documents. Please refer to Section 7.4 for reporting requirements.

6.5 Concomitant Therapy

The use of concomitant medications during the Double-Blind Treatment Period, unless needed to treat an AE, should be the same as the medications used and recorded at Screening (Visit 1) and during the Run-In Period.

All prior and concomitant medications (prescription and over-the-counter), vitamin and mineral supplements, and herbs taken by the subject in the past 30 days will be recorded in the Prior & Concomitant Medication electronic case report form (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.

7 COLLECTION OF STUDY VARIABLES

7.1 Recording of Data

The Investigator will ensure that data collected during this study are recorded in the electronic data capture (EDC) system in the corresponding eCRFs. The Investigator will ensure accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries. Any completed eCRF must be signed by the Investigator. A copy of the completed eCRF will be archived.

7.2 Data Collection Prior to Enrollment

At Screening (Visit 1), the following information will be collected from every participant to identify eligible subjects for further assessments:

- 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
- Medical and surgical history
- Phosphate binder currently used and prescribed daily dose (must be three times a day)
- Physical examination
- Vital signs (pre-dialysis)
- Electrocardiogram evaluation
- Blood sample for clinical laboratory chemistry and hematology tests (pre-dialysis)
- FSH and pregnancy test, if applicable
- Concomitant medications

7.3 Safety Variables

Safety assessments will be performed during the study and will include physical examinations, body weight, vital signs, safety laboratory tests, 12-lead ECG, and AE recording. Body weight, vital signs, 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.

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 or feet), cardiovascular, respiratory, abdomen, lymph nodes, musculoskeletal, and neurological systems. Any findings or absence of findings relative to each subject's physical examination will be carefully documented in the eCRF.

7.3.2 Vital Signs (blood pressure and heart rate)

Blood pressure and heart rate will be obtained at all visits (pre-dialysis). Systolic and diastolic blood pressure will be measured after the subject has been in sitting or supine position for at least 5 minutes. All measurements will be recorded on the source document and in the eCRF.

7.3.3 Electrocardiogram

A 12-lead ECG will be performed after the subject has been in a sitting or supine position for at least 5 minutes.

The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval (uncorrected), QTc-interval (corrected), RR-interval and the Investigator's conclusion on the 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 the Investigator's assessment of all abnormal ECGs will be recorded in the eCRF.

Additional ECGs may be obtained if clinically indicated.

7.3.4 Clinical Laboratory Tests

Samples **must** be obtained, pre-dialysis, for the hematology and chemistry clinical laboratory tests identified in Table 7-1.

Other evaluations and tests performed at Screening (Visit 1) and other visits, as specified in the Schedule of Assessments and Procedures (Section 1.3), will include:

- FSH test, if applicable
- 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 medication.

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 subject to be discontinued from the study, or (3) that requires a subject to receive non-study treatment, or (4) fulfills one or more criteria for serious adverse event (SAE).

Table 7-1: Clinical Laboratory Tests

Hematology[a]	**Chemistry**[b]	**Other**[d]
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[c] Potassium Sodium	FSH Serum pregnancy

[a] Whole blood.
[b] Serum.
[c] Serum phosphorus is also performed separately from standard clinical laboratory tests at protocol-specified time points.
[d] FSH and serum pregnancy tests are performed on all females <60 years of age unless there is a documented method of sterilization, or FSH test confirms post-menopausal status.

7.4 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 subject 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.

Subjects will be monitored throughout the study for AEs, from Screening (Visit 1) through the end of the study. Medical events that occur before Screening (Visit 1) and are ongoing at Screening (Visit 1) should be recorded as medical history, not AEs. All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel such as "Have you had any health problems since the previous visit?", or revealed by observation will be collected and recorded in the AE 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 as specified in the protocol must be recorded on the AE eCRF with the status of the AE noted. Each AE must be followed until it is resolved or stabilized, or until all attempts to determine resolution of the AE are exhausted. All AEs that are ongoing at the end of study will be recorded as ongoing in the eCRF. The procedures specified in Section 7.4.8 are to be followed for reporting SAEs.

7.4.1 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 subjects. For a change in stool form and/or frequency to be considered an AE, the subject must consider the bowel movements to be "bothersome".

7.4.2 Recording Adverse Events

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

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

7.4.3 Assessment of Adverse Events

The relationship of an AE to the study medication (tenapanor or placebo) 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 subject's clinical condition, intercurrent illness, or concomitant medications, and does not follow a known response pattern to the study medication, or the temporal relationship of the event to study medication administration makes a causal relationship unlikely.
- Possibly related: The event follows a reasonable temporal sequence from the time of medication administration, and is possibly due to medication administration and cannot be reasonably explained by other factors such as the subject's clinical condition, intercurrent illness, or concomitant medications.
- Related: The event follows a reasonable temporal sequence from the time of medication administration, and/or follows a known response pattern to the study medication, and cannot be reasonably explained by other factors such as the subject's clinical condition, intercurrent illness, or concomitant medications.

7.4.4 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 AEs.

7.4.5 Discontinuation due to Adverse Events

Any subject who experiences an AE may be withdrawn at any time from the study at the discretion of the Investigator. Subjects 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; refer to Section 8.7. The AE(s) should be noted on the appropriate CRFs and the subject's progress should be followed until the AE is resolved or stabilized. A decision to discontinue a subject due to an AE should be discussed with the Medical Monitor. If the AE may relate to overdose of study medication, the IB should be consulted for details regarding any specific actions to be taken.

7.4.6 Pregnancy

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

The Investigator must report any pregnancy to Medpace Clinical Safety within 1 business day of becoming aware of it. The subject must be immediately discontinued from further treatment with study medication. 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 subjects or in the sexual partners of male subjects from the time the subject 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 subject who received study medication 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 Medpace Clinical Safety.

7.4.7 Serious Adverse Events

An SAE is any AE occurring from Screening through the end of the study, 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 subject 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 Medpace Clinical Safety. See "Reporting Serious Adverse Events" below for details.

7.4.8 Reporting Serious Adverse Events

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

To report an SAE, complete the SAE eCRF in the 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 EDC system, send an email to [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 IRB/Independent Ethics Committee (IEC) in accordance with local requirements. All Investigators involved in trials using the same investigational product will receive 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 subject until the SAE has resolved or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE eCRF in the EDC system for the study and submit any supporting documentation (e.g., subject 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.

7.5 Efficacy Endpoints

Serum phosphorus levels will be measured at all study visits. The primary efficacy endpoint is the change from baseline in s-P level at Week 4. The efficacy of tenapanor as an adjunctive therapy to phosphate binder therapy will be evaluated based on the difference in mean change from baseline in s-P level at Week 4 between the tenapanor and placebo groups.

The following efficacy endpoints will be analyzed as key secondary endpoints:

- s-P response (achieving an s-P level <5.5 mg/dL) at Week 4
- Relative change from baseline in iFGF23 at Week 4, derived as (iFGF23 at Week 4/baseline iFGF23 – 1)
- Relative change from baseline in cFGF23 at Week 4, derived as (cFGF23 at Week 4/baseline cFGF23 – 1)

Other secondary endpoints to be analyzed include:

- Change from baseline in s-P level at Week 1, Week 2, and Week 3
- s-P response at Week 1, Week 2, and Week 3
- Change from baseline in PTH at Week 4

8 METHODOLOGY/STUDY VISITS

8.1 Screening Procedures: Visit 1 (Days -30 to -14)

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

Screening evaluations will consist of the following:

- Assessment of the disease status outlined in the inclusion/exclusion criteria
- Kt/V – the most recent value prior to Screening
- Date of birth, gender, and race
- Weight (pre-dialysis) and height
- Medical and surgical history
- Phosphate binder currently used and prescribed daily dose (must be three times a day)
- Physical examination
- Vital signs (pre-dialysis)
- Electrocardiogram evaluation
- Blood sample for clinical laboratory chemistry and hematology tests (pre-dialysis)
- FSH and pregnancy test, if applicable
- Concomitant medications

Subjects will be instructed not to take any other medications without the approval of the Investigator (except their existing phosphate binder medication). Results of the screening evaluations must meet the inclusion/exclusion criteria for the subject to be enrolled in the study.

8.2 Run-in Procedures: Visit 2 (Days -18 to -7) and Visit 3 (Days -9 to -2)

- Serum phosphorus measurement (pre-dialysis)
- Concomitant medication
- AE assessments

8.3 Visit 4 (Day 1)

- Inclusion/exclusion criteria (assess s-P criteria using the s-P measurement at Visit 3 and confirm other applicable inclusion/exclusion criteria)
- Vital signs (pre-dialysis)
- Serum phosphorus measurement (pre-dialysis)
- Blood collection for biomarker sample (pre-dialysis)
- Blood collection for FGF23 and PTH (pre-dialysis)
- Randomization

- Medical/surgical history (record only changes to medical history from Visit 1)
- Concomitant medications
- Study medication dispensing
- AE assessment

8.4 Visits 5, 6, and 7 (Days 8, 15, and 22 ± 2 Days)

- Serum phosphorus measurement (pre-dialysis)
- Study medication dispensing and/or return, if applicable
- Concomitant medications
- AE assessment

8.5 Visit 8 (Day 29 ± 2 Days)

- Weight (pre-dialysis)
- Vital signs (pre-dialysis)
- Blood collection for biomarker sample (pre-dialysis)
- Blood collection for FGF23 and PTH (pre-dialysis)
- Physical examination
- Electrocardiogram evaluation
- Blood sample for clinical laboratory chemistry and hematology tests (pre-dialysis)
- Blood sample for serum phosphorus (pre-dialysis)
- Pregnancy test (for women of child-bearing potential)
- Study medication return
- Concomitant medication
- AE assessment

8.6 Early Termination Visit

Evaluations scheduled for Visit 8 will be performed at the Early Termination visit for subjects who prematurely discontinue from the study.

8.7 Withdrawal Procedures

In the event of a subject's withdrawal, every effort will be made to complete the End-of-Study assessments (Visit 8). Withdrawn subjects will be followed until resolution of any AEs or until the unresolved AEs are judged by the Investigator to have stabilized.

8.8 Criteria for Study Termination

The study may be terminated at any time by the Sponsor if SAEs occur, or if, in the Sponsor's judgment, there are no further benefits to be achieved from the study, or for administrative reasons. A site may be closed out if the Investigator does not adhere to the protocol. In the event that the clinical development of the investigational product is discontinued, the Sponsor will inform all Investigators/institutions and the IRB overseeing the study.

8.9 Total Blood Volume Required for Study

The approximate blood volume required at scheduled visits for each subject is shown in the following table:

Table 8-1: Approximate Blood Volume per Subject

Test	No. of Samples	Volume Collected for Each Sample (mL)	Total (mL)
Chemistry + b-HCG+ FSH	2	7	14
Hematology (blood)	2	3	6
Phosphorus (serum)	8	4	32
PTH (plasma)	2	4	8
iFGF-23 (plasma)	2	4	8
cFGF-23 (plasma)	2	4	8
Serum biomarkers	2	5	10
Plasma biomarkers	2	6	12
Total	--	--	**98**

8.10 Protocol Deviations

Subjects must fully meet the following criteria in order to be enrolled in the study. In keeping with regulatory requirements, if the Sponsor allows a subject to continue in the study following a protocol deviation, the deviation must be recorded as such.

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 subject, the Investigator, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study inclusion or exclusion criteria
- Failure to comply with dispensing or dosing requirements
- Use of medications, food, drink, herbal remedies, or supplements that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Drug dosing not administered within the time frame specified in the protocol
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examination, 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 medication, failure to update the informed consent form (ICF) when new risks become known, or failure to obtain IRB approvals for the protocol and ICF revisions

At the outset of the study, a process for defining and handling protocol deviations will be established. This will include determining which violations will be designated "critical", requiring immediate notification to the Medical Monitor and the Sponsor. The Investigator is responsible for seeing that all 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. No changes are expected to the primary and secondary efficacy analyses. If the language in this protocol and the language in the SAP differ, the SAP governs. Results obtained from the analyses specified in the final approved version of the SAP will become the basis of the clinical study report for

this study. Any deviations from the final approved version of the SAP will be documented in the clinical study report.

9.2 Determination of Sample Size

Approximately 214 ESRD subjects with hyperphosphatemia will be randomized in a 1:1 ratio to receive either tenapanor or placebo.

The primary endpoint is the change from baseline in s-P level at Week 4. Assuming a common standard deviation of 1.0 mg/dL, a sample size of 214 subjects (107 subjects/group) is expected to provide 95% power to detect a treatment difference of -0.5 mg/dL in the primary endpoint between the tenapanor and placebo groups. This calculation is based on a two-sample *t*-test with a significance level of 0.05 (two-sided) using SAS® PROC POWER. Under the same assumptions stated above, the sample size of 214 subjects will provide at least 85% power at the 0.01 significance level.

9.3 Analysis Populations

The analysis populations defined for this study include: Intent-to-Treat (ITT) population, Full Analysis Set (FAS), Per-Protocol (PP) population, Week 4 Completers, and Safety population.

- Intent-to-Treat Population: will be comprised of all randomized subjects.
- Full Analysis Set: will include all ITT subjects who have at least one post-baseline s-P measurement during the study. It will be the population used for efficacy analyses to be performed with subjects as randomized.
- Per-Protocol Population: will be a subset of the FAS. It will be the analysis population for sensitivity analysis to be performed with subjects as randomized. Any subject who has a significant protocol deviation that could alter his/her efficacy outcome to treatment will be excluded from the PP population.
- Week 4 Completers: will be a subset of the FAS. It will include all FAS subjects who complete the s-P assessment at Week 4. It will be the analysis population for sensitivity analysis to be performed with subjects as randomized.
- Safety Population: will include all ITT subjects who receive at least one dose of the study medication (tenapanor or placebo). It will be the analysis population for safety analyses to be performed with subjects as treated.

9.4 Statistical Methods

9.4.1 General Considerations

All measures will be summarized descriptively by treatment (planned or actually received). Descriptive statistics including the number of observations (n), mean, standard deviation, median, minimum, and maximum will be presented for continuous variables. Summary statistics for iFGF23 and cFGF23 will also include geometric mean and geometric coefficient of variation %. Frequency (n) and percent (%) will be presented for categorical variables.

Individual subject data including relevant derived variables will be listed.

Analyses of efficacy endpoints will be performed on the FAS and the PP population. The statistical testing will be conducted at a significance level of 0.05 (two-sided) unless specified otherwise. Analyses of safety measures will be performed on the Safety population. No statistical testing will be conducted for safety measures.

All data manipulations, descriptive summaries, and statistical hypothesis testing will be performed using SAS®.

9.4.2 Baseline Descriptive Statistics

Baseline characteristics, including demographics, disease characteristics, prior/concomitant medications, and medical/surgical history will be summarized by planned treatment.

9.4.3 Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in s-P level at Week 4. For this continuous endpoint, the following pair of hypotheses will be tested:

$$H_0: \mu_t = \mu_p$$

versus

$$H_1: \mu_t \neq \mu_p$$

where μ_t and μ_p denote the mean changes from baseline in s-P level at Week 4 in tenapanor and placebo groups, respectively. As the primary analysis, the treatment comparison of the mean change will be performed using a mixed-effects model for repeated measures (MMRM) on observed cases of the FAS. The MMRM will include type of phosphate binder (sevelamer or non-sevelamer), s-P level at Visit 3 (<7.5 mg/dL or ≥7.5 mg/dL), treatment, visit (Week 1 through Week 4), treatment-by-visit interaction as fixed effects; baseline (Visit 4) s-P level and baseline-by-visit as covariates; and subject as a random effect. An unstructured (UN) covariance matrix will be used to model the within-subject errors. The least squares mean of

s-P changes within each treatment group will be reported. The difference in mean s-P changes at Week 4 between the tenapanor and placebo groups, along with the 95% confidence interval (CI), 99% CI, and *p*-value will also be reported.

The efficacy of tenapanor as an adjunctive therapy to phosphate binder therapy will be concluded if the estimated difference between the tenapanor and placebo groups in the mean s-P change from baseline at Week 4 is negative (i.e., <0) and the corresponding two-sided *p*-value ≤0.05.

9.4.4 Secondary Efficacy Analyses

For binary response endpoints, the s-P response rate (i.e., the proportion of subjects achieving an s-P level <5.5 mg/dL) at each post-baseline visit will be estimated for each treatment group and be compared between the tenapanor and placebo groups with the 95% and 99% CIs. The *p* value will be obtained from the Cochran-Mantel-Haenszel test adjusting for type of phosphate binder (sevelamer or non-sevelamer) and s-P level at Visit 3 (<7.5 mg/dL or ≥7.5 mg/dL).

The relative change from baseline in iFGF23 (or cFGF23) at Week 4 will be analyzed using an analysis of variance (ANOVA) model with log-transformed relative change at Week 4 as the dependent variable. The model will include type of phosphate binder (sevelamer or non-sevelamer), s-P level at Visit 3 (<7.5 mg/dL or ≥7.5 mg/dL), and treatment as factors. Back-transformed point estimates and CIs (95% and 99%) will be reported.

Mean changes from baseline in s-P level at Week 1, Week 2, and Week 3 will be estimated for each treatment group and be compared between the tenapanor and placebo groups using the MMRM of the primary analysis.

The change from baseline in PTH at Week 4 will be analyzed using an analysis of covariance (ANCOVA) model with PTH change at Week 4 as the dependent variable. The model will include type of phosphate binder (sevelamer or non-sevelamer), s-P level at Visit 3 (<7.5 mg/dL or ≥7.5 mg/dL), treatment as factors and baseline PTH level as a covariate.

9.4.5 Multiple Comparisons / Multiplicity

To control the overall Type I error rate associated with multiple comparisons on the primary and key secondary endpoints at the 0.05 level (two-sided), the following hierarchical testing strategy will be employed:

A. Conduct the statistical testing for the primary comparison between the tenapanor and placebo groups on the primary endpoint "change from baseline in s-P level at Week 4" at the significance level of 0.05 (two-sided).

B. If the result of the primary comparison on the primary endpoint is positive (i.e., estimated mean different <0 and *p*-value ≤0.05), then conduct the statistical testing for the primary comparison between the tenapanor and placebo groups on the key secondary endpoint "s-P response at Week 4" at the significance level of 0.05 (two-sided).

C. If the result of the primary comparison on "s-P response at Week 4" is positive (i.e., estimated rate difference >0 and *p*-value ≤0.05), then conduct the statistical testing for the following two key secondary endpoints using the Hochberg step-up procedure to control the family-wise Type I error rate at the significance level of 0.05 (two-sided):

   - Relative change from baseline in iFGF23 at Week 4
   - Relative change from baseline in cFGF23 at Week 4

Analyses of other secondary endpoints will be descriptive. No multiplicity adjustment will be made for these analyses.

9.4.6 Handling of Missing Data

In the completed clinical study TEN-02-201 conducted by Ardelyx, the rate of missing s-P data was 6.25% (5/80) at both Week 2 and Week 4 visits during the 4-week Randomized Withdrawal Period. The rate of missing s-P data during the 4-week Double-Blind Treatment Period in the current study is expected to be in a similar range. The missing s-P data during the Double-Blind Treatment Period is expected to have limited impact on the study power and the accuracy of estimates for the current study.

The primary endpoint, change from baseline in s-P level at Week 4, will be analyzed using an MMRM on observed cases of the FAS. Changes from baseline in s-P level at Week 1, Week 2, and Week 3 will also be analyzed using the same MMRM on observed cases. To assess the impact of missing s-P data on the primary efficacy outcomes from the MMRM, sensitivity analyses such as ANCOVA using the last-observation-carried-forward (LOCF) imputation approach, completer analysis, and tipping-point analysis will be performed. Details of these sensitivity analyses will be provided in the SAP.

For other endpoints to be analyzed using ANOVA or ANCOVA and all binary response endpoints, missing data will be imputed using the LOCF approach after analysis.

Descriptive summaries of efficacy and safety measures will be based on observed data.

9.4.7 Adjustments for Covariates

In general, the two randomization stratification factors (type of phosphate binder and s-P level at Visit 3) will be adjusted in inferential analyses of efficacy endpoints. Detailed information on covariate adjustment is provided in Sections 9.4.3 and 9.4.4.

9.4.8 Visit Windows

No analysis visit windows will be formally defined. The schedule of assessments and procedures in Section 1.3 details the intended collection of study variables at specified visits. Any additional data collected between scheduled visits will be included in subject data listings but will be excluded from statistical analyses, unless the additional data is used to impute missing data in the analysis.

9.4.9 Safety Analyses

Safety analyses include summaries for AEs, safety laboratory tests, vital signs, body weight, 12-lead ECG, and physical examination.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) will be tabulated by MedDRA system organ class and preferred term. Listings will also be provided for TEAEs.

Other safety measures will be summarized descriptively by treatment and visit.

10 ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will provide direct access to source data and documents for individuals conducting study-related monitoring, audits, IRB/IEC review, and regulatory review. The Investigator must inform the study subject that his/her study-related records may be reviewed by the above individuals without violating the subject's privacy of personal health information in compliance with Health Insurance Portability and Accountability Act of 1996 regulations.

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to 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

Sponsor 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 (CFR §312.50 and §312.56) and the International Conference on Harmonisation (ICH) E6 Guidelines on good clinical practice (Integrated Addendum to ICH E6(R1): Guideline for 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 subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject 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 subject or when the change(s) involve only logistical or administrative aspects of the study and are approved by the Medical Monitor and/or Ardelyx. Any deviation may result in the subject having to be withdrawn from the study and may render that subject non-evaluable.

11.2 Protocol Amendments

Only the Sponsor may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the Sponsor, the Medical Monitor, and Investigators. All amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB prior to their implementation.

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 medical records for the monitor to verify eCRF entries. The Investigator is expected to cooperate with the Sponsor or its designee in ensuring the study adheres to GCP requirements.

The Investigator may not recruit subjects into the study until the Sponsor or its designee has conducted a visit at the site to conduct a detailed review of the protocol and eCRFs and the site has been activated upon Sponsor's approval. With agreement of the Sponsor, attendance at an Investigator meeting may fulfill the Site Initiation requirement.

12 ETHICS

12.1 Institutional Review Board/Independent Ethics Committee Approval

12.1.1 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.

12.1.2 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, subject recruitment procedures, written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB and regulatory authority as applicable.

12.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each subject (or the subject's legally responsible surrogate). Subjects 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 subject (or guardian), prior to any study procedures being performed.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Reporting and Electronic Data Capture

13.1.1 Electronic Case Report Forms (eCRFs)

The Investigator will be provided with eCRFs and will ensure all data from subject 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.

13.1.2 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. Medpace Reference Laboratories (MRL) has been selected to conduct all tests and all samples will be analyzed at MRL. The Investigator must maintain source documents such as laboratory reports and complete history and physical examination reports.

13.1.3 Retention of Source Documents

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

13.2 Retention of Essential Documents

The study essential documents must be maintained as specified in the ICH guidelines to adhere to GCP and applicable regulatory requirements. The Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the Sponsor's responsibility to inform the Investigator or institution as to when these documents no longer need to be retained.

[redacted]

15 REFERENCES

Eknoyam G, Lameire N, Barsoum R, et al. The burden of kidney disease: improving global outcomes, Kidney Int 2005; 66: 1310-1314.

Waheed AA, Pedraza F, Lenz O and Isakova T. Phosphate control in end-stage renal disease: barriers and opportunities, Nephrol Dial Transplant 2013; 28: 2961-2968.

KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD), Kidney Int 2009; 76: S113.

DOPPS Practice Monitor (Dialysis Outcomes and Practice Patterns Study), Arbor Research Collaborative for Health, 2018.

16 SIGNATURES

16.1 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 _____

Date _____

16.2 Sponsor Signature

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

[redacted]

Date