CLINICAL TRIAL PROTOCOL

Study TEN-02-402 (OPTIMIZE)

A Randomized, Open-Label Study to Evaluate the Use of Tenapanor as the Core Therapy in the Treatment of Hyperphosphatemia in Patients with Chronic Kidney Disease on Dialysis who are Phosphate Binder Naïve or on Phosphate Binder Therapy, to Optimize Phosphorus Management (OPTIMIZE)

Protocol Number: TEN-02-402

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Confidentiality Statement

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1 GENERAL INFORMATION

1.1 Study Administrative Structure

A Randomized, Open-Label Study to Evaluate the Use of Tenapanor as the Core Therapy in the Treatment of Hyperphosphatemia in Patients with Chronic Kidney Disease on Dialysis who are Phosphate Binder Naïve or on Phosphate Binder Therapy, to Optimize Phosphorus Management (OPTIMIZE)

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1.2 Synopsis

Protocol Title: A randomized, open-label study to evaluate the use of tenapanor as the core therapy in the treatment of hyperphosphatemia in patients with chronic kidney disease on dialysis who are phosphate binder naïve or on phosphate binder therapy, to optimize phosphorus management (OPTIMIZE)

Sponsor: Ardelyx, Inc.

Study Phase: Phase 4

Objectives: The primary objective of this study is:

- To evaluate the effect of tenapanor alone or in combination with phosphate binders to achieve target serum phosphorus (s-P) levels of ≤5.5 mg/dL when tenapanor is administered as the core therapy (alone or in combination with phosphate binders) for the treatment of hyperphosphatemia in patients with chronic kidney disease (CKD) on dialysis.

The secondary objectives of this study, for the treatment of hyperphosphatemia in CKD patients on dialysis who are phosphate binder naïve or on phosphate binder therapy, include:

- To evaluate the effect of tenapanor alone or in combination with phosphate binders to achieve various s-P levels (e.g., ≤4.5 mg/dL).
- To evaluate different strategies of initiating tenapanor for the control of s-P level.
- To evaluate the effect of different strategies of initiating tenapanor on stool frequency and consistency using a daily eDiary.
- To evaluate the effect of tenapanor on reducing daily phosphorus-lowering therapy pill burden (number of pills and total pill weight) when patients are started on or transitioned to tenapanor from current phosphate binder therapy.
- To evaluate the impact of patient education and use of standard of care medication on the tolerability management of tenapanor.
- To evaluate the tolerability of tenapanor when patients are started on or transitioned to tenapanor from current phosphate binder therapy.
- To evaluate patient experience with phosphorus management routine during study compared to before study.
- To evaluate the effect of tenapanor alone or in combination with phosphate binders on intact fibroblast growth factor 23 (iFGF23) and parathyroid hormone (PTH).
- To evaluate the effect of tenapanor alone or in combination with phosphate binders on the use of PTH-modifying medications

Number of Sites: Approximately 40 sites

Planned Sample Size: Approximately 330 CKD patients on dialysis with hyperphosphatemia (>4.5 mg/dL) will be enrolled in this study.

Study Design: This is a randomized, open-label study to evaluate different methods of initiating tenapanor therapy in CKD patients on dialysis with hyperphosphatemia, when they are either phosphate binder naïve or on phosphate binder therapy.

The study consists of a Screening visit, a 10-week open-label Treatment Period (Part A), and an optional 16-week open-label Extension Period (Part B).

- Patients with s-P >5.5 and ≤10.0 mg/dL under stable phosphate binder treatment are randomized in a 1:1 ratio to two different treatment cohorts:
    - Cohort 1 (straight switch), which stops taking phosphate binders and is started on tenapanor 30 mg twice daily (BID) at Visit 2 (Day 1);
    - Cohort 2, which decreases phosphate binder dose by at least 50% (may be more than 50% if patient is taking an odd number of binder pills each day), with ability to switch the binder regimen from thrice daily (TID) to BID or QD; and initiates tenapanor 30 mg BID at Visit 2 (Day 1).
- Phosphate binder naïve patients with s-P >4.5 and ≤10.0 mg/dL are enrolled as Cohort 3 and receive tenapanor at Visit 2 (Day 1) with a starting dose of 30 mg BID.

The Screening visit (Visit 1) must be scheduled at the first short dialysis interval of the week (Wednesday or Thursday), the Randomization/Enrollment visit (Visit 2) must be scheduled two days after the Screening visit at the second short dialysis interval of the week (Friday or Saturday), and all other visits in the study must be scheduled after a short dialysis interval (Wednesday or Friday for patients on a Monday-Wednesday-Friday schedule and Thursday or Saturday for patients on a Tuesday-Thursday-Saturday schedule provided the patient has not missed any dialysis treatment or altered their schedule). Body weight, vital signs, and blood collections for laboratory assessments **must** be performed pre-dialysis (prior to dialysis at the visit). All other assessments may be performed pre-, during, or post-dialysis but should be performed at the same time at each visit and the same day as dialysis.

The enrollment criteria on s-P will be evaluated based on the s-P measured at the Screening visit (Visit 1) alone (Cohort 3 only: binder naïve) or together with the most recent s-P measurement prior to the Screening visit (Visit 1):

- Patients on phosphate binder therapy must receive phosphate binder(s) thrice daily, and both the s-P level assessed at the most recent measurement prior to the Screening visit (Visit 1) and the s-P level assessed at the Screening visit (Visit 1) must be >5.5

and ≤10.0 mg/dL to qualify for randomization into Cohort 1 or Cohort 2 at Visit 2 (Day 1).

- Phosphate binder naïve patients must have the s-P level assessed at the Screening visit (Visit 1) >4.5 and ≤10.0 mg/dL to qualify for enrollment into Cohort 3 at Visit 2 (Day 1).

Patients who do not meet the randomization/enrollment criteria on s-P will be discontinued as screen failures. Patients must continue to meet all other applicable inclusion/exclusion criteria at Visit 2 (Day 1) in order to be randomized into Cohort 1 or 2 or be enrolled in Cohort 3.

Patients will be educated at Screening (Visit 1) and Randomization/Enrollment (Visit 2) about tenapanor, how to take tenapanor, what they may experience on tenapanor, medications to be discontinued before starting tenapanor, and how best to manage a possible increase in bowel movement frequency and/or loose stool if bothersome (e.g., use of over-the-counter anti-diarrheal), etc.

In order to assess the tolerability profile of tenapanor alone or combined with phosphate binders, patients will use a daily electronic diary (eDiary) to record daily bowel habits (stool frequency and stool consistency) throughout the 10-week Treatment Period, Part A.

On Day 1 (Visit 2), patients will start to receive tenapanor at a dose of 30 mg BID. Tenapanor will be taken orally BID; just prior to breakfast and dinner. Patients should **not** take study drug at the meal immediately preceding hemodialysis. The Investigator may titrate the dose of tenapanor in 10 mg increments down to a minimum of 10 mg QD or up to a maximum of 30 mg BID at any time during the study based on s-P levels and/or gastrointestinal (GI) tolerability.

If a phosphate binder is being taken by a patient in any of the three cohorts, it can be dosed starting at either QD or BID or TID: if taken QD, it should be taken with the largest meal of the day; if taken BID, it should be taken with the same meals tenapanor is taken with. The Investigator may decrease the dose of phosphate binder at any time during the study based on s-P levels. However, dose up-titration for phosphate binder is not allowed from Day 1 (Visit 2) until Week 2 of the Treatment Period (Visit 4). Starting from Visit 4, the Investigator may increase the dose of phosphate binder or add phosphate binder based on s-P levels; the dose of a phosphate binder can be titrated up to the maximum dose TID per the corresponding phosphate binder package insert, if needed, based on s-P levels.

If decreasing the dose of tenapanor or phosphate binder due to low s-P levels, the phosphate binder dose should be decreased prior to decreasing the tenapanor dose until patient is no longer taking any phosphate binder. If increasing the dose of tenapanor or phosphate binder due to high s-P levels, the tenapanor dose should be increased prior to increasing the phosphate binder dose until the tenapanor dose reaches 30 mg BID or cannot be increased due to GI tolerability at the Investigator's discretion.

Recommended dose adjustments based on s-P levels during the study are specified below for each cohort:

In Cohort 1 (straight switch to tenapanor),

- If the patient's s-P assessed at or after Visit 4 (Week 2) is >5.5 mg/dL, the Investigator may add one phosphate binder pill daily (QD) (with largest meal) or one phosphate binder pill BID (at same meals as tenapanor). The phosphate binder dosing regimen should start at QD or BID; and the dose of phosphate binder can be titrated up to the maximum dose TID per the corresponding phosphate binder package insert, if needed. When phosphate binder is being added to Cohort 1, the Investigator should use the phosphate binder the patient stopped at the beginning of the study.
- If the patient is taking phosphate binder and his/her s-P is <5.0 mg/dL, the Investigator may remove one or two phosphate binder pills from the patient's daily regimen.
- If the patient is taking no phosphate binder and his/her s-P is ≤3.5 mg/dL, the dose of tenapanor should be decreased by 10 mg BID. If the patient is taking tenapanor 10 mg BID, then the dose of tenapanor should be decreased to 10 mg QD.

In Cohort 2 (50% phosphate binder reduction),

- The reduced phosphate binder dose can be dosed starting at QD, BID or TID with meals: if taken QD, it should be taken with the largest meal of the day; if taken BID, it should be taken with the same meals tenapanor is taken.
- If the patient's s-P is >5.5 mg/dL, the Investigator may add one phosphate binder pill QD (with largest meal) or one phosphate binder pill BID (at same meals as tenapanor). The dose of phosphate binder can be titrated up to the maximum dose TID per the corresponding phosphate binder package insert, if needed.
- If the patient's s-P is <5.0 mg/dL, the Investigator may remove one or two phosphate binder pills from the patient's daily regimen.
- If the patient is taking no phosphate binder and his/her s-P is ≤3.5 mg/dL, the dose of tenapanor should be decreased by 10 mg BID. If the patient is taking tenapanor 10 mg BID, then the dose of tenapanor should be decreased to 10 mg QD.

In Cohort 3 (phosphate binder naïve),

- If the patient's s-P assessed at or after Visit 4 (Week 2) is >5.5 mg/dL, the Investigator may add one phosphate binder pill QD (with largest meal) or one phosphate binder pill BID (at same meals as tenapanor). The phosphate binder dosing regimen should start at QD or BID; and the dose of phosphate binder can

be titrated up to the maximum dose TID per the corresponding phosphate binder package insert, if needed. The Investigator can choose any brand of phosphate binder.

- If the patient is taking phosphate binder after Visit 4 (Week 2) and his/her s-P assessed after the binder use is <5.0 mg/dL, the Investigator may remove one or more phosphate binder pills from the patient's regimen.
- If the patient is taking no phosphate binder and his/her s-P is ≤3.5 mg/dL, the dose of tenapanor should be decreased by 10 mg BID. If the patient is taking tenapanor 10 mg BID, then the dose of tenapanor should be decreased to 10 mg QD.

Safety assessments will be performed at various time points throughout the study (Schedule of Assessments and Procedures [Part A and Part B] Table 1-1) and will include adverse event (AE) recording, physical examination, body weight, vital signs, 12-lead electrocardiogram (ECG), and safety laboratory tests (routine serum chemistry and hematology). Stool frequency and stool consistency will be collected using a daily eDiary throughout the 10-week Treatment Period (Part A only) as tolerability measures.

Blood samples will be collected to measure s-P, iFGF23, PTH, and clinical laboratory chemistry and hematology tests; additional samples will be stored, as appropriate, for the potential evaluation of exploratory biomarkers.

Treatment Duration

The duration of treatment in this study will be up to 26 weeks; including a 10-week Treatment Period (Part A) and an optional 16-week Extension Period (Part B).

Eligibility Criteria:

Inclusion Criteria:

1. Signed and dated informed consent form 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 and non-lactating.
4. Patients on phosphate binder therapy must be on chronic maintenance hemodialysis (HD) 3 times per 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 patient must meet one of the two dialysis criteria above and been on the new modality of dialysis for a minimum of one month. Phosphate binder naïve patients must be on chronic maintenance HD 3 times per week or chronic maintenance PD.
5. Kt/V ≥1.2 at most recent measurement prior to Screening (Visit 1).
6. Prescribed and taking phosphate binder medication at least 3 times per day or being phosphate binder naïve; defined as

having not taken phosphate binders for at least 3 months prior to Screening. The patient must be taking a minimum of 6 pills per day for Renvela, Auryxia, or PhosLo; and/or a minimum of 3 pills per day for Fosrenol or Velphoro.

7. For patients taking phosphate binders, both the s-P level at the most recent measurement prior to Screening (Visit 1) and the s-P level at Screening (Visit 1) must be >5.5 and ≤10.0 mg/dL.
8. For phosphate binder naïve patients, the s-P level at Screening (Visit 1) must be >4.5 and ≤10.0 mg/dL.
9. Able to understand and comply with the protocol.

Exclusion Criteria:

1. Severe hyperphosphatemia defined as having an s-P level >10.0 mg/dL at any time point during routine clinical monitoring for the 3 preceding months before Screening (Visit 1).
2. Serum/plasma PTH >1200 pg/mL. The most recent value from the patient'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 or irritable bowel syndrome with diarrhea.
5. Scheduled for living donor kidney transplant or plans to relocate to another center during the study.
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 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, 20, and/or 30 mg tablets

Safety, Tolerability, and Efficacy Measures:

Safety Measures:
AE monitoring; physical examination; body weight; vital signs; 12-lead ECG; and safety laboratory tests (routine serum chemistry and hematology)

Tolerability Measures:
Stool frequency and stool consistency collected using a daily eDiary throughout the 10-week Treatment Period (Part A only)

Efficacy Measures:
Serum phosphorus, iFGF23, PTH, medication dose, pill number, pill weight, and other information relative to drug usage (e.g., % on

monotherapy) and patient experience

Statistical Analyses:

Analysis Populations:

- **Intent-to-Treat (ITT) Population:** will include all randomized or enrolled patients.
- **Safety Population:** will include all ITT patients who receive at least one dose of study drug. It will be the analysis population for safety and tolerability analyses.
- **Full Analysis Set (FAS):** will include all ITT patients who meet the study entry eligibility criteria, receive at least one dose of study drug, and have at least one post-baseline s-P measurement during the study. It will be the analysis population for efficacy analyses.
- **FAS (Cohorts 1-2):** will include all FAS patients in Cohort 1 and Cohort 2. It will be the analysis population for analyses of efficacy endpoints applicable to Cohort 1 and Cohort 2 only.

Safety Analyses:
All safety and tolerability measures will be summarized descriptively by cohort and for the entire Safety Population. Treatment-emergent AEs will be summarized by MedDRA system organ class and preferred term. Stool frequency and consistency collected on a daily basis throughout the study will be summarized on a weekly basis (i.e., average weekly stool frequency and average weekly stool consistency).

Efficacy Analyses:
All efficacy measures will be summarized descriptively by cohort and for the entire FAS.

The following efficacy endpoints will be summarized descriptively by cohort and for the entire FAS at each post-baseline visit (only for s-P endpoints), the endpoint visit of the Treatment Period, and the endpoint visit of the entire study:

- s-P response: achieving or maintaining s-P $\leq$5.5 mg/dL
- Normal s-P response: achieving s-P $\leq$4.5 mg/dL
- Borderline s-P response: achieving or maintaining s-P $\leq$6.5 mg/dL
- Change from baseline in s-P
- Relative change from baseline in iFGF23, derived as “change from baseline in iFGF23/baseline iFGF23”
- Change from baseline in PTH
- Change from baseline in total daily dose of PTH-modifying medications (mg)

The following efficacy endpoints will also be summarized descriptively

by cohort and for the entire "FAS (Cohorts 1-2)" at each post-baseline visit, the endpoint visit of the Treatment Period, and the endpoint visit of the entire study for patients switching their phosphate binder therapy to tenapanor therapy:

- Change from baseline in total daily dose of phosphorus-lowering medication (mg) (tenapanor and phosphate binder combined)
- Change from baseline in total daily pill weight (tenapanor and phosphate binder combined)
- Change from baseline in total daily pill number (tenapanor and phosphate binder combined)
- Medication dose response: achieving at least 30% reduction from baseline in total daily dose (mg) of phosphorus-lowering medication
- Pill weight response: achieving at least 30% reduction from baseline in total daily pill weight
- Pill number response: achieving at least 30% reduction from baseline in total daily pill number (e.g., reduce from 6 pills at baseline to ≤4 pills and reduce from 9 pills at baseline to ≤6 pills)
- Pill burden response: achieving pill weight response and pill number response
- s-P and medication dose response: achieving s-P response and medication dose response
- s-P and pill weight response: achieving s-P response and pill weight response
- s-P and pill number response: achieving s-P response and pill number response
- s-P and pill burden response: achieving s-P response, pill weight response, and pill number response
- Normal s-P and medication dose response: achieving normal s-P response and medication dose response
- Normal s-P and pill weight response: achieving normal s-P response and pill weight response
- Normal s-P and pill number response: achieving normal s-P response and pill number response
- Normal s-P and pill burden response: achieving normal s-P response, pill weight response, and pill number response
- Borderline s-P and medication dose response: achieving borderline s-P response and medication dose response
- Borderline s-P and pill weight response: achieving borderline s-P

response and pill weight response

- Borderline s-P and pill number response: achieving borderline s-P response and pill number response
- Borderline s-P and pill burden response: achieving borderline s-P response, pill weight response, and pill number response

The final list of efficacy endpoints will be provided in the statistical analysis plan.

Exploratory inferential analyses may be performed to compare efficacy endpoints between cohorts. Subgroup analyses by age, sex, race, phosphate binder type, baseline s-P, and ending therapy category (e.g., tenapanor alone, tenapanor + ≤3 tablets/day phosphate binder, or tenapanor + >3 tablets/day phosphate binder) will be performed for selective endpoints.

1.3 Schedule of Assessments and Procedures

Table 1-1: Schedule of Assessments and Procedures (Part A and Part B)

Part A - Screening and Treatment Period

	Screening [a]	10-Week Treatment Period [b]							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9[c]
	Day -2	Day 1	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10
Study Day/Visit Window	-2	1[d]	8 ± 2	15 ± 2	22 ± 2	29 ± 2	43 ± 2	57 ± 2	71 ± 2
Study Procedure									
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X [e]							
Randomization/Enrollment		X [a]							
Demographics	X								
Medical/Surgical History	X	X [f]							
Prior/Concomitant Medications [g]	X	X	X	X	X	X	X	X	X
Patient Education [h]	X	X							
eDiary [i] Instructions.	X	X							
eDiary [i] Completion Review			X	X	X	X	X	X	X
Physical Examination	X								X
Weight (pre-dialysis)	X								X
Height	X								
Vital Signs [j]	X								X
12-lead ECG	X								X
Safety Laboratory Evaluations [k]	X								X
Serum Phosphorus	X		X	X	X	X	X	X	X
FSH Test [l]	X								
Pregnancy Test [l]	X								X
Study Drug Dispense		X	X	X	X	X	X	X	X
Study Drug Return/accountability			X	X	X	X	X	X	X
iFGF23, PTH Blood Sample	X								X
Biomarker Blood Sample	X								X
AE Assessment		X	X	X	X	X	X	X	X
Patient Experience Assessment [m]									X

Part B - Optional Extension Period

	16-Week Extension Period [b]				
	Start of Part B Visit 9	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13[c]**
	Week 10	**Week 14**	**Week 18**	**Week 22**	**Week 26**
Study Day/Visit Window	71 ± 2	99 ± 7	127 ± 7	155 ± 7	183 ± 7
Study Procedure					
Prior/Concomitant Medications [g]	X	X	X	X	X
Physical Examination	X				X
Weight (pre-dialysis)	X				X
Vital Signs [j]	X				X
12-lead ECG	X				X
Safety Laboratory Evaluations [k]	X				X
Serum Phosphorus	X	X	X	X	X
Pregnancy Test [l]	X				X
Study Drug Dispense	X	X	X	X	
Study Drug Return/accountability	X	X	X	X	X
iFGF23, PTH Blood Sample	X				X
Biomarker Blood Sample	X				X
AE Assessment	X	X	X	X	X
Patient Experience Assessment [m]	X				

[a] Screening visit will be on the first short interval of the week (Wednesday or Thursday). Randomization/enrollment will be 2 days after the screening visit (Friday or Saturday), if the patient meets all the inclusion/exclusion criteria.
[b] All visits are after a short interval (Wednesday or Friday for M,W,F dialysis and Thursday or Saturday for T, Th, S dialysis)
[c] All assessments and procedures at Visit 9 except study dispensing should be performed at the Early Termination visit for patients who prematurely discontinue from the study before Visit 9; those at Visit 13 should be performed at the Early Termination visit for patients who prematurely discontinue from the study between Visit 9 and Visit 13, if possible.
[d] Day 1 is the randomization/enrollment day and serves as the reference day for all post-randomization visits.
[e] Patients must continue to meet all applicable inclusion/exclusion criteria before randomization/enrollment, including the criteria based on the s-P level at Visit 2.
[f] Record only changes to medical history from Visit 1
[g] Refer to Appendix I for a list of medications to be discontinued before starting tenapanor, prohibited concomitant medications, PTH-modifying medications, and medications recommended for managing changes in bowel movements during the study. These medications will be checked at every visit. Any new PTH-modifying medication use or changes to existing PTH-modifying medication use need to be adequately recorded in the Prior/Concomitant Medications eCRF.
[h] Patient education will include information about tenapanor, how to take tenapanor, what they may experience on tenapanor, medications to be discontinued before starting tenapanor, and how best to manage a possible increase in bowel movement frequency and/or loose stool if bothersome (e.g., use of over-the-counter anti-diarrheal), etc.
[i] The daily eDiary will ask questions about a patient's stool frequency and stool consistency during the past 24 hours. The eDiary is completed during Part A of the study.

[j] Vital signs include sitting or supine blood pressure and pulse, prior to dialysis at the visit.
[k] Safety laboratory evaluations will include the hematology and serum chemistry tests.
[l] 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.
[m] Patient experience assessment will be conducted via an ePRO questionnaire and will include questions regarding a patient's experience with phosphorus management routine during study compared to before study.

1.4 List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransaminase
AST	aspartate aminotransaminase
BID	bis en die, twice a day
BUN	blood urea nitrogen
CFR	Code of Federal Regulations (United States)
CKD	chronic kidney disease
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
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
IBS-C	irritable bowel syndrome with constipation
ICF	informed consent form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
iFGF23	intact fibroblast growth factor 23
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
IUD	intrauterine device
Kt/V	a measure of dialysis adequacy
MedDRA	Medical Dictionary for Drug Regulatory Activities

Abbreviation	Definition
NHE3	sodium-hydrogen exchanger 3
PD	peritoneal dialysis
PR	ECG interval from P wave onset to QRS complex onset
PTH	parathyroid hormone
QD	quaque die, once a day
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
TID	ter in die, three times a day
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). Experimental studies provide support for the epidemiologic findings: phosphate excess promotes vascular calcification, induces endothelial dysfunction and may contribute to other emerging CKD-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. Despite widespread use of phosphate binders, a large proportion of patients do not achieve adequate phosphorus control (DOPPS Practice Monitor 2018). The binding mechanism requires frequent dosing and often, many large pills in order to bind enough dietary phosphorus, and tends to be associated with a significant number of gastrointestinal (GI) side effects including bloating, constipation and nausea. Effectively treated hyperphosphatemia with binders is extremely difficult because of the considerable burden that binders place on patients. In addition to the pill burden and dosing frequency associated with all phosphate binders, the side effect profile with poor 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 effective phosphorus control in ESRD patients. There is, therefore, an unmet medical need to develop oral phosphate-lowering medications with new mechanisms of action, a more manageable dosing and administration regimen, and improved risk-benefit profile.

Tenapanor is an oral, essentially non-absorbed, locally acting inhibitor that targets the sodium/hydrogen exchanger 3 (NHE3), an antiporter expressed on the apical surface of the epithelium of the small intestine and colon. Inhibition of NHE3 by tenapanor results in reduced sodium absorption and consequently, proton retention in cells. This modest intracellular proton retention induces a conformational change in claudin proteins present in tight junctions, reducing permeability specific to phosphate.

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. Blocking NHE3 by tenapanor has no observed effect on serum sodium, nor on the absorption of ions, nutrients, or macromolecules other than dietary sodium and phosphorus.

Results from three Phase 3 studies have demonstrated the efficacy of tenapanor in decreasing s-P levels in adult CKD patients on dialysis with hyperphosphatemia, as both a monotherapy and as a dual-mechanism approach with phosphate binders.

Tenapanor (IBSRELA®) has been approved for the treatment of irritable bowel syndrome with constipation (IBS-C). Tenapanor has been administered to greater than 2800 people including healthy volunteers, patients with IBS-C, CKD with Type 2 diabetes mellitus, and CKD on dialysis. Tenapanor has been evaluated in short term studies up to 900 mg/day and for >20 months at 60 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 10 mg, 20 mg and 30 mg tablets. [redacted]

[redacted]

[redacted]

Dosing consists of one 10 mg, 20 mg or 30 mg tablet, taken orally BID just prior to breakfast and dinner (but not prior to the meal immediately prior to hemodialysis).

Tenapanor tablets, 10 mg, 20 mg and 30 mg, are packaged in an induction sealed, opaque white high-density polyethylene (HDPE) bottle (20 tablets/bottle) with a white polypropylene child resistant closure and 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 control s-P levels in adult patients with CKD on dialysis. Most CKD patients on dialysis 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 2019). Since tenapanor lowers s-P levels via a different mechanism of action, it is believed that tenapanor as monotherapy or combined with current phosphate binder therapy will produce additional phosphorus-lowering activity. This study is designed to investigate different methods of initiating tenapanor therapy in CKD patients on dialysis with hyperphosphatemia.

2.4 Risk-Benefit Assessment

The risk-benefit assessment of tenapanor is based on nonclinical toxicology, safety, and pharmacology studies as well as 25 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 greater than 2800 people including healthy volunteers, patients with IBS-C, CKD with

Type 2 diabetes mellitus, and CKD on dialysis. Tenapanor has been evaluated in short-term studies up to 900 mg/day and for >20 months at 60 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 CKD patients on dialysis 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 patients, sensitive patients 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 patient will be checked at each visit. All patients 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.

Patients 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 potential use of this new therapy, which could improve the treatment of hyperphosphatemia in ESRD patients.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is:

- To evaluate the effect of tenapanor alone or in combination with phosphate binders to achieve target serum phosphorus (s-P) levels of ≤5.5 mg/dL when tenapanor is

administered as the core therapy (alone or in combination with phosphate binder) for the treatment of hyperphosphatemia in patients with CKD on dialysis.

3.2 Secondary Objectives

The secondary objectives of this study, for the treatment of hyperphosphatemia in CKD patients on dialysis who are phosphate binder naïve or on phosphate binder therapy, include:

- To evaluate the effect of tenapanor alone or in combination with phosphate binders to achieve various s-P levels (e.g., ≤4.5 mg/dL).
- To evaluate different strategies of initiating tenapanor for the control of s-P level.
- To evaluate the effect of different strategies of initiating tenapanor on stool frequency and consistency using a daily eDiary.
- To evaluate the effect of tenapanor on reducing daily phosphorus-lowering therapy pill burden (number of pills and total pill weight) when patients are started on or transitioned to tenapanor from current phosphate binder therapy.
- To evaluate the impact of patient education and use of standard of care medication on the tolerability management of tenapanor.
- To evaluate the tolerability of tenapanor when patients are started on or transitioned to tenapanor from current phosphate binder therapy.
- To evaluate patient experience with phosphorus management routine during study compared to before study.
- To evaluate the effect of tenapanor alone or in combination with phosphate binders on iFGF23 and PTH.
- To evaluate the effect of tenapanor alone or in combination with phosphate binders on the use of PTH-modifying medications.

4 STUDY DESIGN

4.1 Design Summary

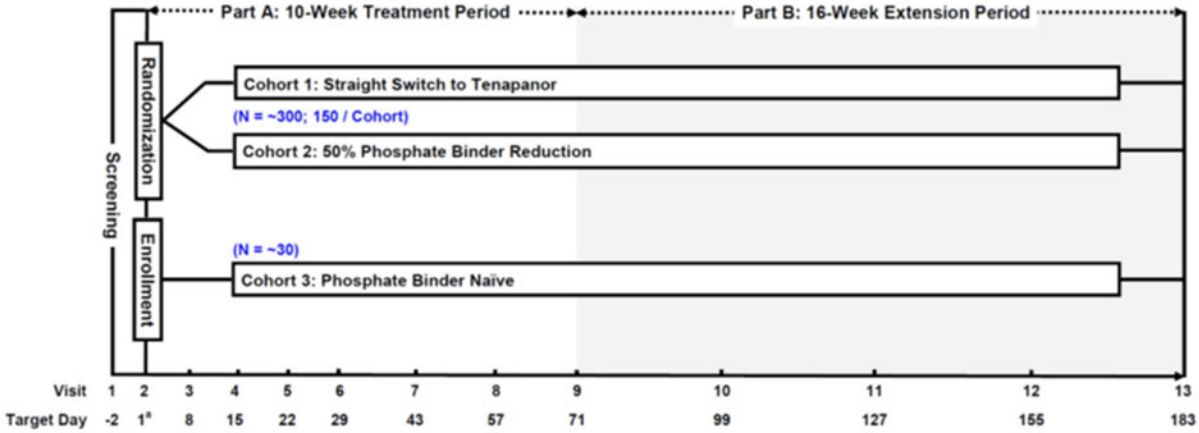
This is a randomized, open-label study to evaluate different methods of initiating tenapanor therapy in CKD patients on dialysis with hyperphosphatemia, when they are either phosphate binder naïve or on phosphate binder therapy. The study consists of a Screening visit, a 10-week open-label Treatment Period (Part A), and an optional 16-week open-label Extension Period (Part B), with a total of three cohorts of patients as shown in Figure 4-1:

- Patients with s-P >5.5 and ≤10.0 mg/dL under stable phosphate binder treatment regimen are randomized in a 1:1 ratio to two different treatment cohorts:

- Cohort 1 (straight switch), which stops taking phosphate binders and is immediately started on tenapanor 30 mg twice daily (BID) at Visit 2 (Day 1);
- Cohort 2, which decreases phosphate binder dose by at least 50% (may be more than 50% if patient is taking an odd number of binder pills each day), with ability to switch the binder regimen from thrice daily (TID) to BID or QD; and initiates tenapanor 30 mg BID at Visit 2 (Day 1).

- Phosphate binder naïve patients with s-P >4.5 and ≤10.0 mg/dL are enrolled as Cohort 3 and receive tenapanor at Visit 2 (Day 1) with a starting dose of 30 mg BID.

Figure 4-1: Study Design Diagram



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

The Screening visit (Visit 1) must be scheduled at the first short dialysis interval of the week (Wednesday or Thursday), the Randomization/Enrollment visit (Visit 2) must be scheduled two days after the Screening visit at the second short dialysis interval of the week (Friday or Saturday), and all other visits in the study must be scheduled after a short dialysis interval (Wednesday or Friday for patients on a Monday-Wednesday-Friday schedule and Thursday or Saturday for patients on a Tuesday-Thursday-Saturday schedule). Body weight, vital signs, and blood collections for laboratory assessments **must** be performed pre-dialysis (prior to dialysis at the visit). All other assessments may be performed pre-, during, or post-dialysis but should be performed at the same time at each visit and the same day as dialysis.

The enrollment criteria on s-P will be evaluated based on the s-P measured at the Screening visit (Visit 1) alone (Cohort 3 only: binder naïve) or together with the most recent s-P measurement prior to the Screening visit (Visit 1):

- Patients on phosphate binder therapy must receive phosphate binder(s) thrice daily, and both the s-P level assessed at the most recent measurement prior to the Screening visit (Visit 1) and the s-P level assessed at the Screening visit (Visit 1) must be >5.5 and ≤10.0 mg/dL to qualify for randomization into Cohort 1 or Cohort 2 at Visit 2 (Day 1).

- Phosphate binder naïve patients must have the s-P level assessed at the Screening visit (Visit 1) >4.5 and ≤10.0 mg/dL to qualify for enrollment into Cohort 3 at Visit 2 (Day 1).

Patients who do not meet the randomization/enrollment criteria on s-P will be discontinued as screen failures. Patients must continue to meet all other applicable inclusion/exclusion criteria at Visit 2 (Day 1) in order to be randomized into Cohort 1 or Cohort 2 or be enrolled in Cohort 3.

Patients will be educated at Screening (Visit 1) and Randomization/Enrollment (Visit 2) about tenapanor, how to take tenapanor, what they may experience on tenapanor, medications to be discontinued before starting tenapanor, and how best to manage a possible increase in bowel movement frequency and/or loose stool if bothersome (e.g., use of over-the-counter anti-diarrheal), etc.

In order to assess the tolerability profile of tenapanor alone or combined with phosphate binders, patients will use a daily eDiary to record daily bowel habits (stool frequency and stool consistency) throughout the 10-week Treatment Period.

On Day 1 (Visit 2), patients will start to receive tenapanor at a dose of 30 mg BID. Tenapanor will be taken orally BID; just prior to breakfast and dinner. Patients should **not** take study drug at the meal immediately preceding hemodialysis. The Investigator may titrate the dose of tenapanor in 10 mg increments down to a minimum of 10 mg QD or up to a maximum of 30 mg BID at any time during the study based on s-P levels and/or GI tolerability.

If a phosphate binder is being taken by a patient in any of the three cohorts, it can be dosed starting at either QD, BID or TID: if taken QD, it should be taken with the largest meal of the day; if taken BID, it should be taken with the same meals tenapanor is taken with. The Investigator may decrease the dose of phosphate binder at any time during the study based on s-P levels. However, dose up-titration for phosphate binder is not allowed from Day 1 (Visit 2) until Week 2 of the Treatment Period (Visit 4). Starting from Visit 4, the Investigator may

increase the dose of phosphate binder or add phosphate binder based on s-P levels; the dose of a phosphate binder can be titrated up to the maximum dose TID per the corresponding phosphate binder package insert, if needed, based on s-P levels.

If decreasing the dose of tenapanor or phosphate binder due to low s-P levels, the phosphate binder dose should be decreased prior to decreasing the tenapanor dose until patient is no longer taking any phosphate binder. If increasing the dose of tenapanor or phosphate binder due to high s-P levels, the tenapanor dose should be increased prior to increasing the phosphate binder dose until the tenapanor dose reaches 30 mg BID or cannot be increased due to GI tolerability at the Investigator's discretion. Details of recommended dose adjustments based on s-P levels are provided in Section 6.1.4.

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. Stool frequency and stool consistency will be collected using a daily eDiary throughout the 10-week Treatment Period (Part A only) as tolerability measures.

Blood samples will be collected to measure s-P, iFGF23, PTH, and clinical laboratory chemistry and hematology tests; additional samples will be stored, as appropriate, for the potential evaluation of exploratory biomarkers.

Approximately 300 CKD patients on dialysis and stable phosphate binder therapy will be randomized in a 1:1 ratio to Cohort 1 or Cohort 2 (~150 patients/cohort); and approximately 30 phosphate binder naïve patients with CKD on dialysis will be enrolled into Cohort 3. Overall, approximately 330 patients will be randomized or enrolled at approximately 40 sites in the United States.

4.1.1 Duration of Study

The treatment duration of this study will be up to 26 weeks including a 10-week Treatment Period (Part A) and an optional 16-week Extension Period (Part B).

5 SELECTION AND WITHDRAWAL OF PATIENTS

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 form (ICF) 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 and non-lactating.
4. Patients on phosphate binder therapy must be on chronic maintenance hemodialysis (HD) 3 times per 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 patient must meet one of the two dialysis criteria above and been on the new modality of dialysis for a minimum of one month. Phosphate binder naïve patients must be on chronic maintenance HD 3 times per week or chronic maintenance PD.
5. Kt/V ≥1.2 at most recent measurement prior to Screening (Visit 1).
6. Prescribed and taking phosphate binder medication at least 3 times per day or being phosphate binder naïve; defined as having not taken phosphate binders for at least 3 months prior to Screening. The patient must be taking a minimum of 6 pills per day for Renvela, Auryxia, or PhosLo; and/or a minimum of 3 pills per day for Fosrenol or Velphoro.
7. For patients taking phosphate binders, both the s-P at the most recent measurement prior to Screening (Visit 1) and the s-P level at Screening (Visit 1) must be >5.5 and 10.0 mg/dL.
8. For phosphate binder naïve patients, the s-P level at Screening (Visit 1) must be >4.5 and ≤10.0 mg/dL.
9. 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 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 at any time point during routine clinical monitoring for the 3 preceding months before Screening (Visit 1).
2. Serum/plasma PTH >1200 pg/mL. The most recent value from the patient'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 or irritable bowel syndrome with diarrhea.
5. Scheduled for living donor kidney transplant or plans to relocate to another center during the study.

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 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. If possible, all assessments and procedures scheduled for Visit 9 except study drug dispensing will be completed at the Early Termination visit for patients who prematurely discontinue from the study before Visit 9; those scheduled for Visit 13 will be completed at the Early Termination visit for patients who prematurely discontinue from the study between Visit 9 and Visit 13 (Section 8.9 and Section 8.10).

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 if the Investigator does not adhere to the protocol or Good Clinical Practice (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 PATIENTS

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 (10 mg), brown (20 mg), red (30 mg), oval, biconvex tablets packaged in HDPE bottles with a desiccant canister. Each bottle contains twenty (20) tablets.

The 10 mg tablets contain 10.6 mg of the tenapanor hydrochloride salt, the 20 mg tablets contain 21.3 mg of the tenapanor hydrochloride salt, and the 30 mg tablets contain 31.9 mg of the tenapanor hydrochloride salt. The 10 mg, 20 mg and 30 mg tablets are oval biconvex film-coated tablets with the following excipients: stearic acid, hydroxypropylcellulose,

microcrystalline cellulose, silicon dioxide, tartaric acid, propyl gallate, hypromellose, triacetin, titanium dioxide and a colorant as described below.

The 10 mg tablets contain yellow iron oxide as the colorant and are yellow in color, the 20 mg tablets contain yellow and red iron oxide as the colorants and are brown in color and the 30 mg tablets also contain red and black iron oxide as the colorants and are red in color.

6.1.2 Identity of Phosphate Binders

Any phosphate binder that is approved for use for the control of hyperphosphatemia in the United States can be administered to patients in this study.

All patients in Cohorts 1 and 2 that need to take phosphate binders as part of this protocol will take the phosphate binder that they were prescribed prior to enrolling in this study. For those in Cohort 3 who need to take phosphate binder as part of this protocol, the choice of binder is up to the Investigator.

6.1.3 Treatments Administered

All patients taking a phosphate binder will take the same phosphate binder that they took prior to enrolling in the study. During the study, phosphate binder can be dosed starting at either QD, BID or TID: if taken QD, it should be taken with the largest meal of the day; if taken BID, it should be taken with the same meals tenapanor is taken with. The dose of a phosphate binder can be titrated up to the maximum dose TID per the corresponding phosphate binder package insert, if needed, based on s-P levels.

All patients will initiate tenapanor therapy at a dose of 30 mg BID. Tenapanor tablets will be taken orally BID, just prior to breakfast and dinner. On dialysis days, patients on HD should not take tenapanor at the meal immediately prior to dialysis and should instead take it just prior to another meal. If a meal is skipped, the dose should be taken with another meal during the day or at around the time that the meal would have been consumed.

6.1.4 Dose Adjustments

The Investigator may titrate the dose of tenapanor in 10 mg increments down to a minimum of 10 mg QD or up to a maximum of 30 mg BID at any time during the study based on s-P levels and/or GI tolerability.

If a phosphate binder is being taken by a patient in any of the three cohorts, it can be dosed starting at either QD, BID or TID: if taken QD, it should be taken with the largest meal of the day; if taken BID, it should be taken with the same meals tenapanor is taken with. The

Investigator may decrease the dose of phosphate binder at any time during the study based on s-P levels. However, dose up-titration for phosphate binder is not allowed from Day 1 (Visit 2) until Week 2 of the Treatment Period (Visit 4). Starting from Visit 4, the Investigator may increase the dose of phosphate binder or add phosphate binder based on s-P levels; the dose of a phosphate binder can be titrated up to the maximum dose TID per the corresponding phosphate binder package insert, if needed, based on s-P levels.

If decreasing the dose of tenapanor or phosphate binder due to low s-P levels, the phosphate binder dose should be decreased prior to decreasing the tenapanor dose until patient is no longer taking any phosphate binder. If increasing the dose of tenapanor or phosphate binder due to high s-P levels, the tenapanor dose should be increased prior to increasing the phosphate binder dose until the tenapanor dose reaches 30 mg BID or cannot be increased due to GI tolerability at the Investigator's discretion.

Recommended dose adjustments based on s-P levels during the study are specified below for each cohort:

In Cohort 1 (straight switch to tenapanor),

- If the patient's s-P assessed at or after Visit 4 (Week 2) is >5.5 mg/dL, the Investigator may add one phosphate binder pill daily (QD) (with largest meal) or one phosphate binder pill BID (at same meals as tenapanor). The phosphate binder dosing regimen should start at QD or BID; and the dose of phosphate binder can be titrated up to the maximum dose TID per the corresponding phosphate binder package insert, if needed. When phosphate binder is being added to Cohort 1, the Investigator should use the phosphate binder the patient stopped at the beginning of the study.

- If the patient is taking phosphate binder and his/her s-P is <5.0 mg/dL, the Investigator may remove one or two phosphate binder pills from the patient's daily regimen.

- If the patient is taking no phosphate binder and his/her s-P is ≤3.5 mg/dL, the dose of tenapanor should be decreased by 10 mg BID. If the patient is taking tenapanor 10 mg BID, then the dose of tenapanor should be decreased to 10 mg QD.

In Cohort 2 (50% phosphate binder reduction),

- The reduced phosphate binder dose can be dosed starting at QD, BID or TID with meals: if taken QD, it should be taken with the largest meal of the day; if taken BID, it should be taken with the same meals tenapanor is taken with.

- If the patient's s-P is >5.5 mg/dL, the Investigator may add one phosphate binder pill QD (with largest meal) or one phosphate binder pill BID (at same time as tenapanor). The dose of phosphate binder can be titrated up to the maximum dose TID per the corresponding phosphate binder package insert, if needed.

- If the patient's s-P is <5.0 mg/dL, the Investigator may remove one or two phosphate binder pills from the patient's daily regimen.

- If the patient is taking no phosphate binder and his/her s-P is ≤3.5 mg/dL, the dose of tenapanor should be decreased by 10 mg BID. If the patient is taking tenapanor 10 mg BID, then the dose of tenapanor should be decreased to 10 mg QD.

In Cohort 3 (phosphate binder naïve),

- If the patient's s-P assessed at or after Visit 4 (Week 2) is >5.5 mg/dL, the Investigator may add one phosphate binder pill QD (with largest meal) or one phosphate binder pill BID (at same meal as tenapanor). The phosphate binder dosing regimen should start at QD or BID; and the dose of phosphate binder can be titrated up to the maximum dose TID per the corresponding phosphate binder package insert, if needed. The Investigator can choose any brand of phosphate binder.

- If the patient is taking phosphate binder after Visit 4 (Week 2) and his/her s-P assessed after the binder use is <5.0 mg/dL, the Investigator may remove one or more phosphate binder pills from the patient's regimen.

- If the patient is taking no phosphate binder and his/her s-P ≤3.5 mg/dL, the dose of tenapanor should be decreased by 10 mg BID. If the patient is taking tenapanor 10 mg BID, then the dose should be decreased to 10 mg QD.

6.1.5 Method of Assigning Patients to Treatment Groups

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

Specifically for patients on phosphate binder therapy, a stratified randomization scheme will be employed, with type of phosphate binder (sevelamer, calcium-based binder, iron-based

binder, other non-sevelamer binder, or a combination of binders of different types) and s-P level at Visit 1 (<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 GCP standards. After meeting all of the inclusion/exclusion criteria, eligible patients on phosphate binder therapy will be randomized in a 1:1 ratio at Visit 2 (Day 1) to Cohort 1 or Cohort 2.

The randomization of this study will be implemented via an Interactive Response Technology (IRT). The IRT will allocate the cohort and provide the randomization number. The IRT will provide the appropriate number of bottles of tenapanor.

If a patient 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 drug is stored and dispensed in accordance with the label and 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 bottle label.

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 their representative, including but not limited to, lot number, expiration date, amount received, and the disposition of all study drug. Current dispensing records will also be maintained including the date and amount of study drug dispensed and the patient receiving study drug. All remaining study drug 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 Drug

Tenapanor tablets will be supplied as yellow (10 mg), brown (20 mg), red (30 mg), oval, biconvex tablets packaged in HDPE bottles with a desiccant canister. Each bottle contains twenty (20) tablets.

Tenapanor tablets should be stored in the original packaging according to the bottle label.

6.3.2 Blinding Methods

This is an open-label study.

6.4 Prior and Concomitant Therapy

All prior and concomitant medications (prescription and over-the-counter), vitamin and mineral supplements, and herbs taken by the patient in the past 30 days will be recorded in the Prior/Concomitant Medications electronic case report form (eCRF) and will include start and end dates, dose and route of administration, frequency, and indication. Medications taken for a procedure should also be included.

To mitigate the impact of possible GI side effects with tenapanor, non-study medications that may increase bowel movement frequency and/or loosen stool must be discontinued before starting tenapanor and prohibited during the study. At each visit, patients will be questioned whether they are receiving any of these medications; if the answer is yes, patients will be instructed to stop these medications.

For patients experiencing an increase in bowel movement frequency and/or looser stool after receiving tenapanor, non-study medications such as over-the-counter anti-diarrheal may be recommended for managing these GI side effects.

The use of PTH-modifying medications during the study will be checked at every visit. Any new PTH-modifying medication use or changes to existing PTH-modifying medication use need to be adequately recorded in the Prior/Concomitant Medications eCRF.

The complete lists of prohibited medications and recommended medications for managing GI side effects of tenapanor as well as the list of common PTH-modifying medications can be found in Appendix I.

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. Completed eCRFs must be signed by the Investigator and copies of the completed eCRFs will be archived.

7.2 Data Collection Prior to Enrollment

At Screening (Visit 1), the following information will be collected from every patient to assess the patient's eligibility for further assessments:

- Assessment of disease status outlined in the inclusion/exclusion criteria
- Date of birth, sex, race, ethnicity
- 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 samples for s-P, iFGF23, PTH, clinical laboratory chemistry and hematology tests, and biomarker analysis (pre-dialysis)
- FSH and pregnancy test, if applicable
- eDiary (instructions and beginning of data entry for stool frequency and consistency)
- Prior/concomitant medications; special attention should be given to medications to be discontinued before starting tenapanor (see Appendix I). Any use of PTH-modifying medications in the past 30 days need to be adequately recorded in the Prior/Concomitant Medications eCRF.
- Patient education on information about tenapanor, how to take tenapanor, what they may experience on tenapanor, medications to be discontinued before starting tenapanor, and how best to manage a possible increase in bowel movement frequency and/or loose stool if bothersome (e.g., use of over-the-counter anti-diarrheal), etc

7.3 Tolerability and Safety Measures

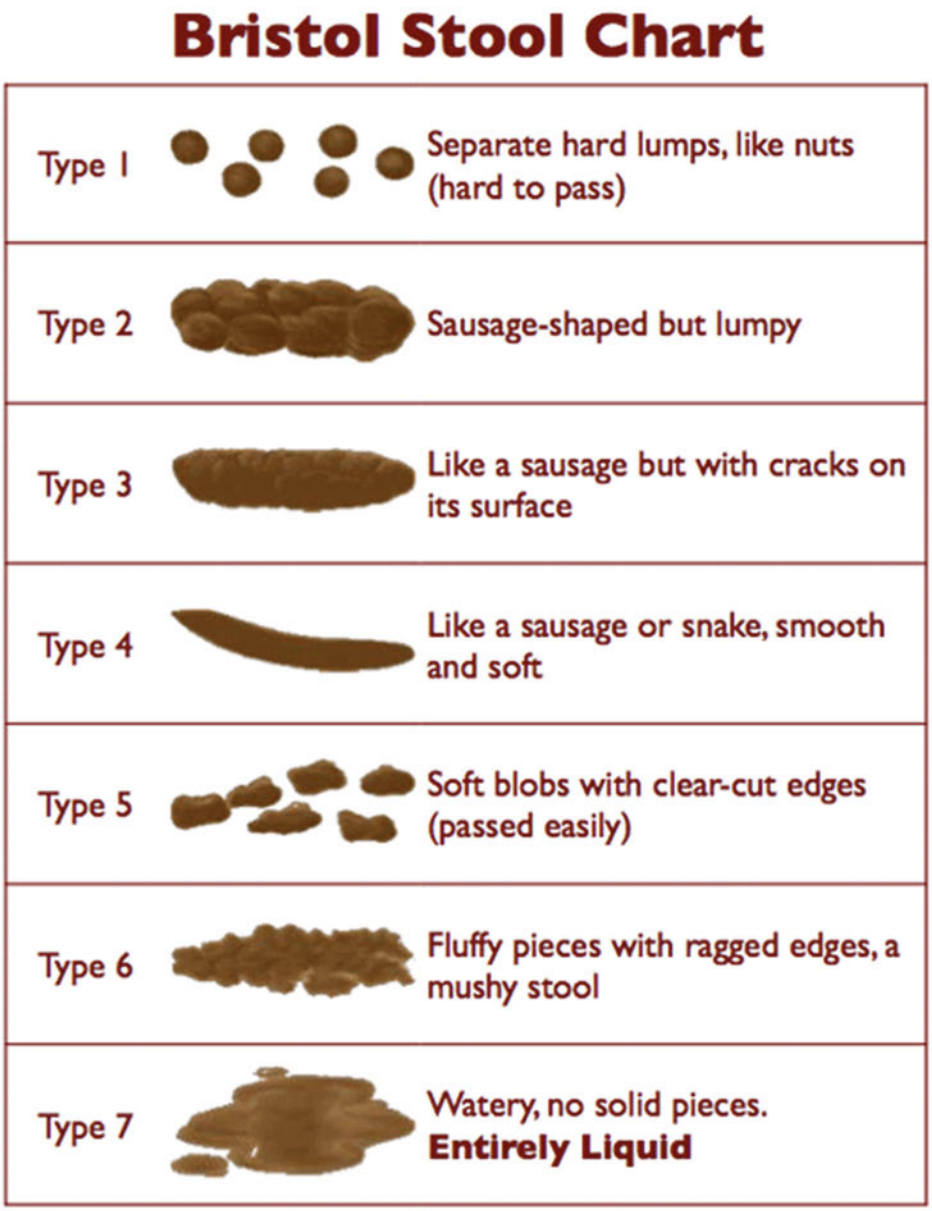
Stool frequency and stool consistency will be collected using a daily eDiary throughout the 10-week Treatment Period (Part A only) as tolerability measures. Safety assessments will be performed during the study and will include physical examination, body weight, vital signs, 12-lead ECG, safety laboratory tests, and AE recording. Body weight, vital signs, and blood collections for laboratory assessments **must** be performed pre-dialysis (prior to dialysis at the visit). All other assessments may be performed pre-, during, or post-dialysis but should be performed at the same time at each visit and the same day with dialysis.

7.3.1 Stool Frequency and Consistency

Patients will use an eDiary (an electronic device application) every day between 5:00 PM and 11:59 PM (local time) from Screening (Visit 1) through the end of Part A (Visit 9/Early Termination).

Patients will answer questions via eDiary about the number of bowel movements they have each day and the stool consistency for each bowel movement assessed by the Bristol Stool Form Scale shown in Figure 7-1.

Figure 7-1: Bristol Stool Form Scale (Lewis 1997)



7.3.2 Physical Examination

The physical examination will be performed at Screening (Visit 1), Visit 9/Early Termination (end of Part A), and Visit 13/Early Termination (end of Part B) and 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 patient's physical examination will be carefully documented in the eCRF.

7.3.3 Body Weight and Vital Signs (blood pressure and heart rate)

Body weight, blood pressure and heart rate will be obtained pre-dialysis at Screening (Visit 1), Visit 9/Early Termination (end of Part A), and Visit 13/ Early Termination (end of Part B). Systolic and diastolic blood pressure will be measured after the patient 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.

7.3.4 Electrocardiogram

A 12-lead ECG will be performed at Screening (Visit 1), Visit 9/Early Termination (end of Part A), and Visit 13/ Early Termination (end of Part B) after the patient 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 interpretation on the ECG profile.

The Investigator will assess whether the ECG is normal or abnormal; abnormalities will be further classified as 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 and recorded as an unscheduled visit.

7.3.5 Clinical Laboratory Tests

Samples **must** be obtained, pre-dialysis, on the day of the visit for all 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

7.3.5.1 Analysis of Clinical Laboratory Tests

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

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 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	Serum pregnancy iFGF23 [e] PTH [e]

[a] Whole blood.
[b] Serum.
[c] Serum phosphorus is 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.
[e] Plasma

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.

Patients 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 patient 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.

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 7.4.7 are to be followed for reporting SAEs.

7.4.1 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 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 with study drug (Tenapanor or phosphate binder) due to AEs will be categorized as dose not changed, dose reduced, drug interrupted, drug withdrawn, or not applicable. Other actions taken due to AEs will be categorized as required concomitant medication, required concomitant procedure, discontinued from study, 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.

7.4.2 Assessment of Adverse Events

The relationship of an AE to the study drug (tenapanor or phosphate binder) 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 medications, 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 medications.
- 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 medications.

7.4.3 Following Adverse Events

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

7.4.4 Discontinuation due to Adverse Event

Any patient who experiences an AE may be withdrawn at any time from the study at the discretion of the Investigator. For each patient withdrawn from the study due to an AE, whether serious or non-serious, the AE should be noted on the Adverse Events CRF and should be followed until the AE is resolved or stabilized, the condition becomes chronic in nature, all attempts to determine resolution of the AE are exhausted, or the patient dies. 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 drug, the IB should be consulted for details regarding any specific actions to be taken.

7.4.5 Pregnancy

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

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

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

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 InClin Safety.

7.4.6 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 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 InClin Safety. See “Reporting Serious Adverse Events” below for details.

7.4.7 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 InClin Drug Safety within 24 hours of the knowledge of the occurrence.

To report an SAE, complete the study specific Serious Adverse Event Report Form and email [redacted] The SAE information will be entered into the EDC system and the AE will marked as "serious". This will trigger an email notification alert to the team that an SAE has occurred.

Reconciliation of SAE information in the EDC with the SAE information received and entered in the Argus database will be performed per the InClin Data Management Plan.

Safety Contact Information:

[redacted]

[redacted] Investigator is required to submit SAE reports to the IRB/Independent Ethics Committee (IEC) in accordance with local requirements. All Investigators currently involved in clinical trials of tenapanor will receive safety alert notifications for submission to their local IRB/IEC as required. All reports sent to Investigators will blind the treatment assignment.

Follow-Up of SAE:

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

7.5 Efficacy Endpoints

Efficacy measures in this study include s-P (to be measured at all scheduled visits except Visit 2), iFGF23, PTH, medication dose, pill number, pill weight, and other information relative to drug usage (e.g., % on monotherapy), and patient experience.

The following efficacy endpoints will be analyzed by cohort and for the entire FAS at each post-baseline visit (only for s-P endpoints), the endpoint visit of the Treatment Period, and the endpoint visit of the entire study:

- s-P response: achieving or maintaining s-P ≤5.5 mg/dL
- Normal s-P response: achieving s-P ≤4.5 mg/dL
- Borderline s-P response: achieving or maintaining s-P ≤6.5 mg/dL
- Change from baseline in s-P
- Relative change from baseline in iFGF23, derived as "change from baseline in iFGF23/baseline iFGF23"
- Change from baseline in PTH
- Change from baseline in total daily dose of PTH-modifying medications (mg)

The following efficacy endpoints will also be analyzed by cohort and for the entire "FAS (Cohorts 1-2)" at each post-baseline visit. the endpoint visit of the Treatment Period, and the endpoint visit of the entire study:

- Change from baseline in total daily dose of phosphorus-lowering medication (mg) (tenapanor and phosphate binder combined)
- Change from baseline in total daily pill weight (tenapanor and phosphate binder combined)
- Change from baseline in total daily pill number (tenapanor and phosphate binder combined)
- Medication dose response: achieving at least 30% reduction from baseline in total daily dose (mg) of phosphorus-lowering medication
- Pill weight response: achieving at least 30% reduction from baseline in total daily pill weight
- Pill number response: achieving at least 30% reduction from baseline in total daily pill number (e.g., reduce from 6 pills at baseline to ≤4 pills and reduce from 9 pills at baseline to ≤6 pills)
- Pill burden response: achieving pill weight response and pill number response
- s-P and medication dose response: achieving s-P response and medication dose response
- s-P and pill weight response: achieving s-P response and pill weight response
- s-P and pill number response: achieving s-P response and pill number response
- s-P and pill burden response: achieving s-P response, pill weight response, and pill number response
- Normal s-P and medication dose response: achieving normal s-P response and medication dose response
- Normal s-P and pill weight response: achieving normal s-P response and pill weight

response

- Normal s-P and pill number response: achieving normal s-P response and pill number response
- Normal s-P and pill burden response: achieving normal s-P response, pill weight response, and pill number response
- Borderline s-P and medication dose response: achieving borderline s-P response and medication dose response
- Borderline s-P and pill weight response: achieving borderline s-P response and pill weight response
- Borderline s-P and pill number response: achieving borderline s-P response and pill number response
- Borderline s-P and pill burden response: achieving borderline s-P response, pill weight response, and pill number response

The final list of efficacy endpoints will be provided in the statistical analysis plan (SAP).

8 METHODOLOGY/STUDY VISITS

8.1 Patient Education

A patient education program will be used as a standard method to educate patients on tenapanor at Screening (Visit 1) and Randomization/Enrollment (Visit 2) and will include the following information:

- Basic information about tenapanor
- How to take tenapanor
- Possible increased bowel movement frequency and/or looser stool with tenapanor, and reason for these potential changes
- What to expect if changes in stool frequency and stool form occur with tenapanor
    - When likely to occur
    - How long likely to last (transient)
    - Severity (mild to moderate)
    - Most patients remain in “normal” range
    - Most patients stay on therapy

The patient education program will also include specific guidance on how to manage the side effect profile of tenapanor and include the following information:

- Ensure patient has stopped taking any stool softener, laxative, magnesium, or

lubricant before starting tenapanor

- Provide recommendation to take Imodium or other over-the-counter anti-diarrheal medicine, if needed

All patient-facing educational materials will be approved by the IRB prior to use.

8.2 Patient Experience Assessment

Patients will be asked about their experience with phosphorus management routine during study compared to before study. The assessment will be conducted via an ePRO questionnaire at Visit 9/Early Termination (end of Part A).

8.3 Screening Procedures: Visit 1 (Day -2)

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

Screening evaluations will consist of the following:

- Assessment of disease status outlined in the inclusion/exclusion criteria
- Date of birth, sex, race, and ethnicity
- Weight (pre-dialysis) and height (kg and cm, respectively)
- Kt/V – the 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 samples for s-P, iFGF23, PTH, clinical laboratory chemistry and hematology tests, and biomarker analysis (pre-dialysis)
- FSH and pregnancy test, if applicable
- eDiary (instructions and beginning of data entry for stool frequency and consistency)
- Prior/concomitant medications; special attention should be given to medications to be discontinued before starting tenapanor (see Appendix I). Any use of PTH-modifying medications in the past 30 days need to be adequately recorded in the Prior/Concomitant Medications eCRF.

- Patient education on information about tenapanor, how to take tenapanor, what they may experience on tenapanor, medications to be discontinued before starting tenapanor, and how best to manage a possible increase in bowel movement frequency and/or loose stool if bothersome (e.g., use of over-the-counter anti-diarrheal), etc

Patients will be instructed not to take any other medications without the approval of the Investigator. Results of the screening evaluations must meet the inclusion/exclusion criteria for the patient to continue in the study.

8.4 Treatment Period: Visit 2 (Day 1)

- Inclusion/exclusion criteria (assess s-P criteria using the s-P measurement at Visit 1 and confirm other applicable inclusion/exclusion criteria)
- Randomization (Cohorts 1-2) or enrollment (Cohort 3)
- Medical/surgical history (record only changes to medical history from Visit 1)
- eDiary (instructions and review of data entry for stool frequency and consistency; reinforce the need to complete daily)
- Prior/concomitant medications; special attention should be given to medications to be discontinued before starting tenapanor (see Appendix I). Any new PTH-modifying medication use or changes to existing PTH-modifying medication use since Screening need to be adequately recorded in the Prior/Concomitant Medications eCRF.
- Patient education
- Study drug dispensing
- AE assessment

8.5 Treatment Period: Visits 3, 4, 5, 6, 7 and 8 (Days 8, 15, 22, 29, 43, and 57 ± 2 Days)

- Serum phosphorus measurement (pre-dialysis)
- eDiary (review data entry and reinforce the need to complete daily)
- Study drug dispensing and/or return, if applicable
- Concomitant medications; special attention should be given to prohibited concomitant medications (see Appendix I). Any new PTH-modifying medication use or changes to existing PTH-modifying medication use since the previous assessment of concomitant medications need to be adequately recorded in the Prior/Concomitant Medications eCRF.

- AE assessment

8.6 End of Treatment Period or Start of Extension Period: Visit 9 (Day 71 ± 2 Days)

- Weight (pre-dialysis)
- Physical examination
- Vital signs (pre-dialysis)
- Electrocardiogram evaluation
- Blood samples for s-P, iFGF23, PTH, clinical laboratory chemistry and hematology tests, and biomarker analysis (pre-dialysis)
- Pregnancy test (for women of child-bearing potential)
- Study drug dispensing and/or return, if applicable
- eDiary (review data entry)
- Patient experience assessment
- Concomitant medications; special attention should be given to prohibited concomitant medications (see Appendix I). Any new PTH-modifying medication use or changes to existing PTH-modifying medication use since the previous assessment of concomitant medications need to be adequately recorded in the Prior/Concomitant Medications eCRF.
- AE assessment

8.7 Optional Extension Period: Visits 10, 11, and 12 (Days 101, 131, and 161 ± 7 Days)

- Serum phosphorus measurement (pre-dialysis)
- Study drug dispensing and/or return, if applicable
- Concomitant medications; special attention should be given to prohibited concomitant medications (see Appendix I). Any new PTH-modifying medication use or changes to existing PTH-modifying medication use since the previous assessment of concomitant medications need to be adequately recorded in the Prior/Concomitant Medications eCRF.
- AE assessment

8.8 End of Extension Period: Visit 13 (Day 191 ± 7 Days)

- Weight (pre-dialysis)
- Physical examination
- Vital signs (pre-dialysis)

- Electrocardiogram evaluation
- Blood samples for s-P, iFGF23, PTH, clinical laboratory chemistry and hematology tests, and biomarker analysis (pre-dialysis)
- Pregnancy test (for women of child-bearing potential)
- Study drug return
- Concomitant medications; special attention should be given to prohibited concomitant medications (see Appendix I). Any new PTH-modifying medication use or changes to existing PTH-modifying medication use since the previous assessment of concomitant medications need to be adequately recorded in the Prior/Concomitant Medications eCRF.
- AE assessment

8.9 Early Termination Visit

If possible, all assessments and procedures scheduled for Visit 9 (Section 8.6) except study drug dispensing will be completed at the Early Termination visit for patients who prematurely discontinue from the study before Visit 9; those scheduled for Visit 13 (Section 8.8) will be completed at the Early Termination visit for patients who prematurely discontinue from the study between Visit 9 and Visit 13.

8.10 Withdrawal Procedures

In the event of a patient's withdrawal for any reason, every effort will be made to complete the Early Termination visit. At the Early Termination visit, assessments and procedures scheduled for the last scheduled visit in Part A (Visit 9; except study drug dispensing) or Part B (Visit 13) will be performed and are dependent upon whether the patient's withdrawal occurs in Part A or Part B (Section 8.9).

Each withdrawn patient with ongoing AE(s) at study withdrawal will be followed until the AE(s) are resolved or stabilized, the condition becomes chronic in nature, all attempts to determine resolution of the AE(s) are exhausted, or the patient dies.

8.11 Criteria for Study Termination

The study may be terminated at any time by the Sponsor for reasons including but not limited to the following: (i) if SAEs occur, (ii) if, in the Sponsor's judgment, there are no further benefits to be achieved from the study, or (iii) 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 shall inform all Investigators/institutions participating in the study conduct and the IRB overseeing the study.

8.12 Total Blood Volume Required for Study

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

Table 8-1: Approximate Blood Volume per Patient (Parts A and B Combined)

Test	No. of Samples	Volume Collected for Each Sample (mL)	Total (mL)
Chemistry + FSH	3	7	21
Hematology (blood)	3	3	9
Phosphorus (serum)	12	4	48
PTH (plasma)	3	4	12
iFGF-23 (plasma)	3	4	12
Serum biomarkers	3	5	15
Plasma biomarkers	3	6	18
Total	**--**	**--**	**135**

8.13 Protocol Deviations

Patients must fully meet the eligibility criteria in order to be enrolled in the study. 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, the Investigator, or site staff. Examples of deviations include, but are not limited to:

- Enrolling a patient that does not meet study eligibility criteria
- Use of medications, food, drink, herbal remedies, or supplements that are specifically prohibited in the protocol (see Appendix I)
- Missed or out-of-window visits
- Study drug not administered per protocol
- Failure to adhere to the schedule of assessments

- Failure to comply with regulatory requirements for patient safety

A process for defining and handling protocol deviations will be established for this study. The process will include the definition of "critical" protocol deviation and steps for immediate notification of the "critical" protocol deviation to the Medical Monitor and the Sponsor. The Investigator is responsible for seeing that all known protocol deviations are recorded and handled appropriately.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Plan

A formal SAP will be provided separately. 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 300 CKD patients on dialysis and stable phosphate binder therapy will be randomized in a 1:1 ratio to Cohort 1 or Cohort 2 (~150 patients/cohort); and approximately 30 phosphate binder naïve patients with CKD on dialysis will be enrolled into Cohort 3. Overall, approximately 330 patients with CKD on dialysis will be randomized or enrolled in this study. The sample size of this study is not planned based on statistical considerations.

9.3 Analysis Populations

The analysis populations defined for this study include: Intent-to-Treat (ITT) population, Safety Population, Full Analysis Set (FAS), and FAS (Cohorts 1-2).

- Intent-to-Treat Population: will be comprised of all randomized or enrolled patients.
- Safety Population: will include all ITT patients who receive at least one dose of study drug. It will be the analysis population for safety and tolerability analyses.
- Full Analysis Set: will include all ITT patients who meet the study entry eligibility criteria, receive at least one dose of study drug, and have at least one post-baseline s-P measurement during the study. It will be the population used for efficacy analyses.
- Full Analysis Set (Cohorts 1-2): will include all FAS patients in Cohort 1 and Cohort 2. It will be the population used for analyses of efficacy endpoints applicable to Cohort 1 and Cohort 2 only.

9.4 Statistical Methods

9.4.1 General Considerations

All measures will be summarized descriptively by cohort. 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 will also include geometric mean and geometric coefficient of variation %. Frequency (n) and percent (%) will be presented for categorical variables.

Individual patient data including relevant derived variables will be listed.

Analyses of efficacy endpoints will be performed on the FAS and subsets of FAS. Analyses of safety and tolerability measures will be performed on the Safety population. The statistical testing, if any, will be conducted at a significance level of 0.05 (two-sided).

9.4.2 Baseline Descriptive Statistics

Baseline characteristics, including demographics, disease characteristics, prior/concomitant medications, and medical/surgical history will be summarized by cohort and overall for relevant analysis set(s).

9.4.3 Efficacy Analysis

All efficacy measures and endpoints will be descriptively summarized at each visit by cohort and for the corresponding analysis set.

For response endpoints, the response rate at each post-baseline visit will be estimated with asymptotic 95% confidence interval for each cohort. For exploratory purposes, inferential analyses may be performed for comparisons of continuous and binary endpoints between cohorts. No multiplicity adjustment will be implemented.

Subgroup analyses by age, sex, race, phosphate binder type, baseline s-P, and ending therapy category (e.g., tenapanor alone, tenapanor + ≤3 tablets/day phosphate binder, or tenapanor + >3 tablets/day phosphate binder) will also be performed for selective endpoints.

Analyses will be detailed in the SAP.

9.4.4 Handling of Missing Data

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

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

9.4.5 Adjustments for Covariates

In general, the two randomization stratification factors (type of phosphate binder and s-P level at Visit 1) will be adjusted in inferential analyses of efficacy endpoints on FAS (Cohorts 1-2). Baseline value may also be adjusted if applicable. Detailed information on covariate adjustment will be provided in the SAP.

9.4.6 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. Data collected at a scheduled visit will be used as the data at the corresponding analysis visit even if the visit is out-of-window. To minimize the amount of missing data, data collected at an unscheduled visit will be mapped to an analysis visit based on analysis windows if data at the corresponding scheduled visit are not available. Similarly, data from the Early Termination visit may also be mapped. Detailed information on analysis windows will be provided in the SAP.

9.4.7 Safety and Tolerability Analyses

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

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

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

As a tolerability analysis, stool frequency and consistency collected on a daily basis throughout the 10-week Treatment Period will be summarized (for Part A only) on a weekly basis (i.e., average weekly stool frequency and average weekly stool consistency).

9.4.8 Interim Analysis

This is an open-label study. No formal interim analysis is planned for this study. Informal summaries of key measures based on preliminary data will be performed on an ongoing basis.

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 will contact the Sponsor immediately if contacted by a regulatory agency about a site inspection.

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 Health Insurance Portability and Accountability Act of 1996.

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

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

11.1 Conduct of Study

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof (Tokyo 2004), and in accordance with the FDA Code of Federal Regulations (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 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 or when the change(s) involve only logistical or administrative aspects of the study and are approved by the Medical Monitor. 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.

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. Monitoring visits can occur remotely, if necessary.

The Investigator will provide access to the source documents or provide certified copies of 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 patients into the study until the Sponsor or its designee has conducted a detailed review of the protocol and eCRFs with the site staff and the site has been activated upon the 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, 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.

12.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each patient (or the patient's legally responsible surrogate). 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).

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 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.

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

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

14 ADMINISTRATIVE INFORMATION

14.1 Financing and Insurance

Financing and insurance will be addressed in a separate agreement between the Sponsor and the Investigator.

14.2 Publication Policy

Ardelyx, Inc. will retain ownership of all data. All proposed publications based on this study will be subject to the Sponsor's approval requirements.

15 REFERENCES

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

Lewis S and Heaton K. Stool form scale as useful guide to intestinal transit time, Scand J Gastroenterol 1997; 32: 920-924.

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 _____

Investigator's Printed Name:

Investigational Site or Name of Institution:

Date _____

16.2 Sponsor Signature

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

[redacted]

Date

APPENDIX I: USE OF PRIOR AND CONCOMITANT MEDICATIONS

Prohibited Medications:

To mitigate the impact of possible GI side effects with tenapanor, the following non-study medications that may increase bowel movement frequency and/or loosen stool must be discontinued before starting tenapanor and must be prohibited during the study:

- Stool softener
- Laxatives
- Magnesium
- Lubricants

At each visit, patients will be questioned whether they are receiving any of these medications; if the answer is yes, patients will be instructed to stop these medications.

Recommended Medications for Managing Changes in Bowel Movements:

For patients experiencing an increase in bowel movement frequency and/or looser stool after receiving tenapanor, the following non-study medications may be recommended for managing these changes to bowel movements:

- Over-the-counter anti-diarrheal medicine (e.g., Imodium)

Reporting of PTH-Modifying Medications:

The use of PTH-modifying medications during the study including, but not limited to the following, will be checked with each patient at every visit, and if taken, be adequately recorded in the Prior/Concomitant Medications eCRF:

- Calcitriol (1,25-dihydroxycholecalciferol)
- Hecterol (doxercalciferol)
- Parsabiv (etelcalcetide)
- Sensipar (cinacalcet)
- Zemplar (paricalcitol)