Study Title: PA-ADPKD-304: A Phase 3, Open-label, Roll-over Study to Assess Long-term Safety of Lixivaptan in Participants With Autosomal Dominant Polycystic Kidney Disease Who Completed Study PA-ADPKD-303: The ALERT Study

ClinicalTrials.gov ID: NCT05208866

Clinical Study Protocol Version 2.0, dated 20-May-2022

Clinical Study Protocol Version 2.0, dated 20-May-2022, Summary of Changes

CLINICAL STUDY PROTOCOL

PA-ADPKD-304: A Phase 3, Open-label, Roll-over Study to Assess Long-term Safety of Lixivaptan in Participants with Autosomal Dominant Polycystic Kidney Disease Who Completed Study PA-ADPKD-303: The ALERT Study

Protocol Number: PA-ADPKD-304

IND Number: 136,419

Sponsor:	Palladio Biosciences, Inc. 5 Walnut Grove Drive Suite 120 Horsham, PA 19044
Sponsor Contact:	Neil Shusterman, MD FACP Chief Medical Officer Palladio Biosciences, Inc. 5 Walnut Grove Drive, Suite 120 Horsham, PA 19044 Email: nshusterman@palladiobio.com
Medical Monitor:	Joyce Johnsrud, MD ICON Clinical Research Email: Joyce.Johnsrud@iconplc.com In a study related health emergency, when the assigned medical monitor cannot be reached, please refer to Section 7.2.8.3 for further contact information.
Version of Protocol:	2.0
Date of Protocol:	20-MAY-2022

CONFIDENTIAL

PROTOCOL APPROVAL - SPONSOR SIGNATURE

Protocol Title	PA-ADPKD-304: A Phase 3, Open-label, Roll-over Study to Assess Long-term Safety of Lixivaptan in Participants with Autosomal Dominant Polycystic Kidney Disease Who Completed Study PA-ADPKD-303: The ALERT Study
Protocol Number	PA-ADPKD-304
Protocol Version	2.0
Protocol Date	20 MAY 2022

Protocol accepted and approved by:

Neil H. Shusterman, MD FACP
Chief Medical Officer
Palladio Biosciences, Inc.
5 Walnut Grove Drive
Suite 120
Horsham, PA 19044

Signature

20May2022
Date

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol titled "PA-ADPKD-304: A Phase 3, Open-label, Roll-over Study to Assess Long-term Safety of Lixivaptan in Participants with Autosomal Dominant Polycystic Kidney Disease Who Completed Study PA-ADPKD-303: The ALERT Study"

Protocol Number: PA-ADPKD-304

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the protocol, the ICH harmonized tripartite guideline E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry, the Declaration of Helsinki, and all applicable government regulations. I will not make changes to the protocol before consulting with Palladio Biosciences or implement protocol changes without Institutional Review Board (IRB)/Ethics Committee (EC) approval except to eliminate an immediate risk to participants. I agree to administer study treatment only to participants under my personal supervision or the supervision of a Sub-Investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Palladio Biosciences.

Signature of Investigator Date

Printed Name of Investigator

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PROTOCOL SYNOPSIS

Protocol Number:	PA-ADPKD-304
Protocol Title:	PA-ADPKD-304: A Phase 3, Open-label, Roll-over Study to Assess Long-term Safety of Lixivaptan in Participants with Autosomal Dominant Polycystic Kidney Disease Who Completed Study PA-ADPKD-303: The ALERT Study
Sponsor:	Palladio Biosciences, Inc. 5 Walnut Grove Drive Suite 120 Horsham, PA 19044
Study Phase:	Phase 3
Study Sites:	Up to approximately 25 US sites
Indication:	Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Rationale:	ADPKD is the most frequent inherited cause of end-stage renal failure. Animal models have shown that vasopressin activity is necessary for the disease to manifest and progress. Studies of the vasopressin V_2 receptor antagonist tolvaptan have shown that it can slow the progression of renal function deterioration in patients with ADPKD. However, serious drug induced liver injury (DILI) occurs in a certain percentage of patients treated with tolvaptan, requiring diligent testing of liver chemistry in all patients and discontinuation of the drug when the test results are elevated in order to prevent serious outcomes. The vasopressin V_2 receptor antagonist, lixivaptan, has also been shown to ameliorate polycystic disease manifestations in animal models of disease. Evidence from Quantitative Systems Toxicology modeling and initial clinical results suggest that lixivaptan does not have the same potential for liver injury. Thus, lixivaptan may represent a safer alternative to tolvaptan with similar efficacy. The ALERT Study (PA-ADPKD-303) is a Phase 3, open-label study of lixivaptan in participants who experienced abnormal liver chemistry test results on tolvaptan resulting in permanent discontinuation of tolvaptan. This roll-over study is designed to provide these participants with continued access to lixivaptan as well as allow for the assessment of long-term safety and efficacy of lixivaptan in this population.
Objectives:	The primary objective of this study is: • To assess the hepatic safety of lixivaptan with continued dosing. The secondary objectives of this study are: • To characterize the non-hepatic safety and tolerability of lixivaptan; • To assess renal function (efficacy) in participants while on lixivaptan using change in estimated glomerular filtration rate (eGFR).
Participant Population:	The following are requirements for entry into the study at Visit 1: **Inclusion criteria:** 1. Male or female participants with ADPKD who completed study PA-

ADPKD-303

2. Female participants must:
    a. not be pregnant, lactating, or breastfeeding.
    b. be either postmenopausal (defined as amenorrhea for ≥ 12 months), surgically sterile (defined as having undergone hysterectomy and/or bilateral oophorectomy), or if of child-bearing potential (WOCBP) must agree to continue to practice appropriate methods of birth control or remain abstinent (only if this is the usual and preferred lifestyle of the participant) during the full duration of the study and for 30 days after the last dose of lixivaptan treatment. Acceptable forms of contraception include the following:
        - hormonal contraceptives (i.e., oral, intravaginal, transdermal, injectable, implantable)
        - intrauterine device (IUD), including progestin-containing intrauterine devices
        - intrauterine hormone-releasing system (IUS)
        - male sexual partner who has been vasectomized for at least 3 months prior to Screening and who has obtained a follow-up negative sperm count and is the sole sexual partner
        - bilateral tubal ligation
        - Essure® procedure (tubal occlusion)
        - male or female condom with spermicide (cream, spray, gel, suppository, or polymer film)
        - diaphragm, cervical cap, or contraceptive sponge with spermicide (with or without a male condom)
3. Male participants must agree to continue to use an acceptable form of birth control (see list above) or remain abstinent (only if this is the usual and preferred lifestyle of the participant) during the full duration of the trial and for 30 days after the last dose of lixivaptan treatment
4. Continued control of hypertension without the use of a diuretic in concert with KDIGO "Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease"
5. Continued adherence to prohibitions on concomitant medications stated in the study PA-ADPKD-303 protocol and in Section 5.7.1.2 of this protocol, including use of strong or moderate CYP3A4 or CYP2C8 inhibitors or inducers
6. Read, understood, and provided written informed consent after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures.

Exclusion criteria:

	1. Any contraindication to continued treatment with lixivaptan 2. Clinically significant (CS) incontinence, overactive bladder, or urinary retention (e.g., benign prostatic hyperplasia) 3. New York Heart Association Functional Class 3 or 4 heart failure or other significant cardiac or electrocardiogram (ECG) findings that could pose a safety risk to the participant 4. Hypovolemia on physical examination at Screening 5. The following laboratory results based on serum drawn at Visit 24 of PA-ADPKD-303: a. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values >1.5 × upper limit of normal (ULN) b. Total bilirubin values >1.5 × ULN 6. eGFR <20 ml/min/1.73 m^2 based on laboratory results from Visit 26 of PA-ADPKD-303 7. A finding at Screening that precludes safe participation in the study or participants who are likely to be non-compliant with study procedures in the opinion of the Investigator or medical monitor.
Study Design:	This is a Phase 3, open-label, roll-over study to demonstrate the continued hepatic and non-hepatic safety and renal efficacy of lixivaptan in participants with ADPKD who previously experienced abnormal liver chemistry test results while treated with tolvaptan, were permanently discontinued from the drug for that reason, and subsequently completed study PA-ADPKD-303, the open-label lead-in study with lixivaptan. Up to 50 participants can be enrolled and treated with lixivaptan in study PA-ADPKD-303. All participants completing the lead-in study and meeting eligibility criteria for this study will be able to enroll. It is estimated that approximately up to 40 participants will enroll in this study, assuming 90% of participants complete study PA-ADPKD-303 and 90% meet eligibility and elect to enroll in this study. The Screening period will be 4 weeks in duration. Assessments completed during the final 4 visits (Visits 24, 25, 26, and 27) of the lead-in study will serve as the screening and baseline assessments for this study. Visit 27 of the lead-in study will also serve as Visit 1 of this study. Liver chemistry tests assessed at Visit 24 and eGFR assessed at Visit 26 of the lead-in study will be used for assessment of laboratory-related eligibility criteria at Visit 1 of this study. Safety assessments (e.g., ECG, physical examination) performed at Visits 25, 26, and 27 of the lead-in study will also be used for assessment of eligibility and will constitute the baseline values for this study. The mean of the eGFR values obtained at Visits 25, 26, and 27 of the lead-in study will be used to determine the baseline eGFR value for this study. Evaluation of eligibility will be completed at Visit 1 of this study, following signing of informed consent. Participants satisfying all study entry criteria at Visit 1 will be considered enrolled following completion of all Visit 1 study procedures and will be dispensed lixivaptan treatment in accordance with Table 1 to start the Lixivaptan Re-titration Period. During the 1-to-2-week Lixivaptan Re-titration Period, participants whose

	final dose during the Maintenance Period of the lead-in study was 100 mg BID or less will remain on that dose for one week and then proceed to the Maintenance Treatment Period. Participants on doses greater than 100 mg BID will be directly titrated to their final dose of the lead-in study during a second week in the re-titration period (See Table 1). Lixivaptan treatment titration and assignment will be programmed into the Interactive Response Technology (IRT) system. Participants will continue on lixivaptan treatment for up to 104 weeks during the Maintenance Period and will be assessed at a study visit every 12 weeks where study procedures will include clinical laboratory determinations, including liver chemistry panels. In between the quarterly study visits, participants will be required to have blood drawn for liver chemistry determinations every 4 weeks. Where available and approved, visits designated as "laboratory only" visits may be conducted remotely by a home healthcare clinician or by a designated third-party that will process samples for shipment to the central laboratory. In addition, liver chemistry tests may be drawn in the clinic if that is more convenient for the participant. At the end of 104 weeks, lixivaptan treatment will be stopped, and participants will enter a 4-week Follow-up Period during which final assessments will be obtained over 3 visits starting on the 8th day following the last dose of lixivaptan treatment and continuing through the 28th day.

Study Period Description and Estimated Duration:

Screening Period: The Screening Period will be 4 weeks in duration. Screening values for assessment of eligibility for enrollment will be those obtained during the final 4 visits (Visits 24, 25, 26 and 27) of study PA-ADPKD-303. Evaluation of eligibility will be initiated following the signing of the informed consent for this study (V27 of PA-ADPKD-303/V1 of PA-ADPKD-304). Participants satisfying all study entry criteria at Visit 1 will be considered enrolled following completion of all Visit 1 study procedures and will be dispensed lixivaptan 100 mg BID to start the Lixivaptan Re-titration Period. Participants whose last dose in the lead-in study was 50 mg BID, can enter this roll-over study on that dose. These participants will be dispensed 50 mg BID at Visit 1 to start the Lixivaptan Re-titration Period and remain on that dose for one week.

Lixivaptan Re-titration Period: Titration of lixivaptan will occur over a 1-to-2-week re-titration period. Following one week of dosing, the dose of lixivaptan will be increased from 100 mg BID to the final dose taken at the end of the Maintenance Period for those participants whose final dose at the end of the lead-in study was greater than 100 mg BID. Participants whose final dose was 100 mg BID or less in study PA-ADPKD-303, will proceed directly to Visit 3 following one week of re-titration.

Table 1. Dose Titration Based on Dose Achieved at End of Maintenance Period in Lead-in Study PA-ADPKD-303

Final Dose in study PA-ADPKD-303	Week 1	Week 2
100 mg BID	100mg BID	N/A
150 mg BID	100mg BID	150mg BID
150/100 mg (AM/PM)	100mg BID	150/100mg (AM/PM)
200 mg BID	100mg BID	200mg BID
200/150 mg (AM/PM)	100mg BID	200/150mg (AM/PM)

*Participants whose dose was reduced to 50 mg BID during the lead-in study, may continue on that dose in this study following one week of re-titration. For those participants dosing will be one (1) 50 mg capsule twice daily

Maintenance Treatment Period: Following completion of the Lixivaptan Re-titration Period, participants will continue into the open-label Maintenance Treatment Period following completion of Visit 3 assessments for up to 104 weeks. Participants will be assessed at study visits scheduled every 12 weeks but will have required liver chemistry testing every 4 weeks; those visits occurring between the 12-week study visits are designated as "laboratory-only visits". Where available and approved, the laboratory-only visits may be conducted remotely by a Home Healthcare Clinician (HHC) or by a designated third-party that will process samples for shipment to the central laboratory. In addition, liver chemistry tests may be drawn in the clinic if that is more convenient for the participant. The 12-week study visits at Weeks 12, 36, 60 and 84 can be performed either on-site or remotely by

<table>
<tr><td></td><td>an HHC, if available and approved.

Follow-up Period: Three (3) visits will occur over 4 weeks following the last dose of lixivaptan in order to obtain final assessments. Starting with the 8th day after the last dose of lixivaptan, serum creatinine will be drawn at 3 time points (no less than 24 hours apart between each sampling) over a period of up to 28 days post last dose of lixivaptan.

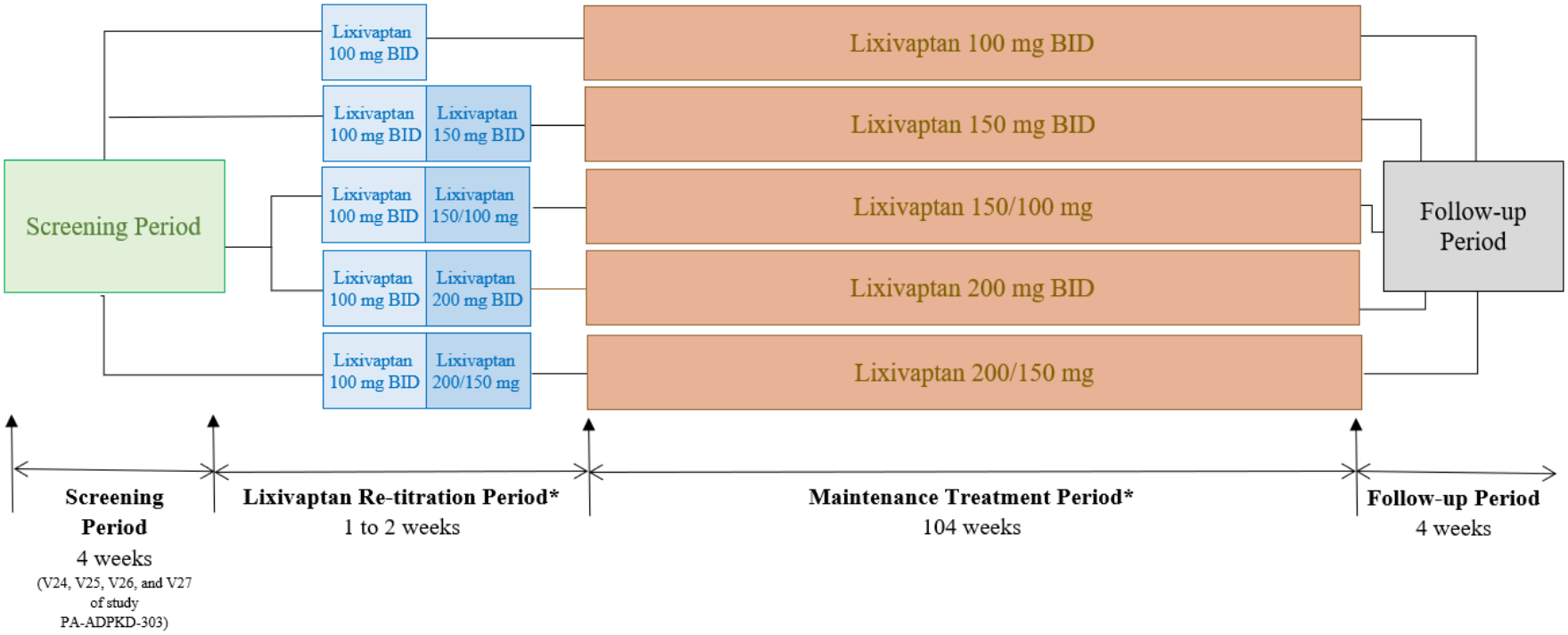
The total duration of participation in this study from the signing of ICF at Visit 1 will be approximately 109 to 110 weeks.</td></tr>
<tr><td>Lixivaptan Treatment, Dosage, and Route of Administration:</td><td>The sponsor (Palladio Biosciences, Inc.) will supply lixivaptan 50 mg capsules for use during the study. Participants will take 2 to 4 capsules BID, dependent on the final dose from the Maintenance Period of study PA-ADPKD-303. All doses will be self-administered by participants orally at home.

Table 2. Dosing Diagram
<table>
<tr><th>Dose Level*</th><th>AM Dose</th><th>50mg Capsules per Administration</th><th>PM Dose</th><th>50mg Capsules per Administration</th></tr>
<tr><td>2**</td><td>100 mg</td><td>2</td><td>100 mg</td><td>2</td></tr>
<tr><td>3</td><td>150 mg</td><td>3</td><td>150 mg</td><td>3</td></tr>
<tr><td>3a***</td><td>150 mg</td><td>3</td><td>100 mg</td><td>2</td></tr>
<tr><td>4</td><td>200 mg</td><td>4</td><td>200 mg</td><td>4</td></tr>
<tr><td>4a****</td><td>200 mg</td><td>4</td><td>150 mg</td><td>3</td></tr>
</table>
*Participants whose dose was reduced to 50 mg BID during the lead-in study, may continue on that dose in this study. For those participants dosing will be one (1) 50 mg capsule twice daily. In the event of newly emerging tolerability issues while on the 50 mg BID dose, the participant will be discontinued.
**Participants on Level 2 who require a dose reduction as a result of newly emerging tolerability issues or treatment-emergent AEs can have their dose reduced to 50 mg BID if approved by the medical monitor.
***Participants having difficulty tolerating Dose Level 3 can drop back to 150 mg in the AM and 100 mg in the PM (Dose Level 3a: 150/100 mg).
****Participants having difficulty tolerating Dose Level 4 can drop back to 200 mg in the AM and 150 mg in the PM (Dose Level 4a: 200/150 mg).</td></tr>
<tr><td>Study Assessments:</td><td>Safety: Liver chemistry tests (ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase), clinical laboratory parameters (hematology, non-hepatic clinical chemistry, and urinalysis), 12-lead ECGs, vital signs, physical examination, adverse events (AEs), and serious adverse events (SAEs).
Efficacy: eGFR</td></tr>
<tr><td>Criteria for Evaluation:</td><td>Primary Endpoint
Safety:
Proportion of participants with serum ALT levels >3 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent Hepatic Events Review Committee (HERC) to be at least</td></tr>
</table>

	probably related to lixivaptan and resulted in discontinuation of lixivaptan treatment. **Secondary Endpoints** *Safety:* Proportion of participants with serum ALT levels >5 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in discontinuation of lixivaptan treatment. Proportion of participants with serum ALT levels >3 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in dose reduction of lixivaptan treatment. Safety and tolerability of lixivaptan assessed through evaluation of AEs, clinical laboratory findings (clinical chemistry including additional analyses of liver chemistry tests, hematology, and urinalysis), vital signs, and 12-lead electrocardiograms (ECGs). *Efficacy:* Change in annualized eGFR from baseline (mean of 3 eGFR determinations obtained at Visits 25, 26, and 27 of study PA-ADPKD-303) to final assessment (mean of 3 eGFR determinations obtained during the Follow-up Period).
Statistical Methods:	**Populations for Analysis:** Enrolled Population: The Enrolled Population is defined as all participants who meet all eligibility criteria during the Screening Period and complete Visit 1. All general summaries, except safety and efficacy analyses are based on the Enrolled Population, unless specified otherwise. Safety Population: The Safety Population is a subset of the Enrolled Population defined as those participants who received at least 1 dose of lixivaptan. This population will be utilized for all safety analyses. Efficacy Population: The Efficacy Population is a subset of the Safety Population defined as those participants who have at least 1 eGFR determination during the Screening Period (Follow-up Period of study PA-ADPKD-303) and have at least 1 eGFR determination during the Follow-up Period of this study. This population will be used for all efficacy analyses. **Primary Hepatic Safety Analysis:** Descriptive statistics (n, percentage and 95% confidence intervals) will be used to present the proportion of participants with serum ALT levels >3 × ULN that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in discontinuation of lixivaptan treatment during the Lixivaptan Re-titration or Maintenance Treatment Periods. **Secondary Hepatic Safety Analyses:** Similarly, descriptive statistics (n, percentage and 95% confidence intervals)

	will be utilized to present the 2 secondary endpoints: 1) the proportion of participants with serum ALT levels >5 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in the discontinuation of lixivaptan treatment; and 2) the proportion of participants with serum ALT levels >3 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in lixivaptan dose reduction. **Additional Hepatic Safety Analyses:** Proportion of participants who develop any of the following abnormalities during the Lixivaptan Re-titration or Maintenance Treatment Periods: • >3 ×, 5 ×, 10 ×, and 20 × ULN elevations for ALT • >3 ×, 5 ×, 10 ×, and 20 × ULN elevations for AST • >3 ×, 5 ×, 10 ×, and 20 × ULN elevations for either ALT or AST • ALT or AST levels >2 × their baseline • Any elevation of total bilirubin >2 × ULN • Any elevation of alkaline phosphatase >2 × ULN • Elevation of aminotransferase (>3 × ULN) accompanied by elevated bilirubin (>2 × ULN) and displayed as evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots • Elevation of aminotransferase in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue • Possible liver-related deaths and liver-related treatment discontinuations. **Additional Non-hepatic Safety Analyses:** The following safety variables will be summarized using appropriate descriptive statistics: Treatment-emergent adverse events, clinical laboratory data, vital signs, and 12-lead ECGs. Potentially clinically significant results in certain clinical laboratory tests, 12-lead ECGs, and vital signs identified using prospectively defined criteria will also be summarized descriptively. **Efficacy Analysis:** Baseline eGFR is defined as the mean of the 3 eGFR assessments obtained during the Screening Period (Visits 25, 26, and 27 of study PA-ADPKD-303.) The endpoint eGFR is defined as the mean of 3 eGFR assessments obtained during the Follow-up Period of this study. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for the change from baseline in annualized eGFR at endpoint.

Figure 1. Study Schema



*Eligible participants whose final dose was 50 mg BID at the end of study PA-ADPKD-303 can continue on that dose in this study and will be re-titrated over one week during the Lixivaptan Re-titration Period, prior to initiating the Maintenance Treatment Period.

Table 3. Schedule of Procedures

Assessment	Screening Period[a]				Lixivaptan Re-titration Period[b]		Maintenance Treatment Period			Follow-up Period[c]		
	(4 weeks + 3 days)				Telehealth Visit[e]	Clinic or Remote Visit[f]	Laboratory Only Visits[d] (every 4 weeks ± 5 days)	Study Visits (every 12 weeks ± 5 days)	EoT/ ET Visit (Week 104 ± 5 Days)	Laboratory Only Visits[d]		Study Visits
					(1 to 2 weeks ± 3 days)		(104 weeks ± 3 days)			(Up to 4 weeks ± 3 days)		
Study Week	(Week -6 to Week -2)				(Week -1 to Week 0)		Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92, 100	Weeks 12[f], 24, 36[f], 48, 60[f], 72, 84[f], 96[f]	Week 104	Day 8 + 3 days after last dose	Day 12 to 24 days after last dose	Day 28 ± 3 days after last dose
	PA-ADPKD-303 Study											
Visit Number	V24	V25	V26	V27/ [V1][a]	(V2[e])	V3/ Last[f]	V4, V5, V7, V8, V10, V11, V13, V14, V16, V17, V19, V20, V22, V23, V25, V26, V28	V6[f], V9, V12[f], V15, V18[f], V21, V24[f], V27[f]	V29/ET	V30	V31	V32
Informed consent				[X]								
Review eligibility (Inclusion/Exclusion)				[X]								
Vital signs[g]	X			X		X		X	X			X
Body weight[h]	X					X		V15	X			X
Physical examination[i]	X			X				V9, V15, V21	X			X
ECG	X			X				V9, V15, V21	X			X
Pregnancy test (WOCBP only)[j]	X			X		X		X	X			X
Urinalysis	X			X				V15	X			X
Hematology	X			X		X		V9, V15, V21	X			
Chemistry Blood Sample[k]	X			X								
Complete Chemistry Panel	X			X		X		X	X			X
Liver Chemistry Panel	X			X		X	X	X	X			X

Assessment	Screening Period[a]				Lixivaptan Re-titration Period[b]		Maintenance Treatment Period			Follow-up Period[c]		
	(4 weeks + 3 days)				Telehealth Visit[e]	Clinic or Remote Visit[f]	Laboratory Only Visits[d] (every 4 weeks ± 5 days)	Study Visits (every 12 weeks ± 5 days)	EoT/ ET Visit (Week 104 ± 5 Days)	Laboratory Only Visits[d]		Study Visits
					(1 to 2 weeks ± 3 days)		(104 weeks ± 3 days)			(Up to 4 weeks ± 3 days)		
Study Week	(Week -6 to Week -2)				(Week -1 to Week 0)		Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92, 100	Weeks 12[f], 24, 36[f], 48, 60[f], 72, 84[f], 96[f]	Week 104	Day 8 + 3 days after last dose	Day 12 to 24 days after last dose	Day 28 ± 3 days after last dose
	PA-ADPKD-303 Study											
Visit Number	V24	V25	V26	V27/ [V1][a]	(V2[e])	V3/ Last[f]	V4, V5, V7, V8, V10, V11, V13, V14, V16, V17, V19, V20, V22, V23, V25, V26, V28	V6[f], V9, V12[f], V15, V18[f], V21, V24[f], V27[f]	V29/ET	V30	V31	V32
Serum Creatinine		X	X							X	X	
Lixivaptan dispensation				X		X		X				
Lixivaptan compliance and reconciliation					X	X		X	X			
IRT entry				X	X	X	X	X	X			X
Adverse events	<---------->			<---------->								
Assess for liver dysfunction	<---------->				<----------							
Prior and concomitant medications	<---------->			<----------								

ECG = electrocardiogram; EoT = End of treatment; ET = Early termination visit; IRT = interactive response technology system; Last = Last re-titration visit; V = Visit; WOCBP = women of childbearing potential

Shaded assessments (Visit 24, Visit 25, Visit 26) denote PA-ADPKD-303 assessments that will not be included as part of screening and/or baseline values for study PA-ADPKD-304 ;[ ] = denotes assessment not part of PA-ADPKD-303 Follow-up Period V27; ( ) = Not all participants will need these visits.

[a] Results from assessments completed during the final 4 visits (Visits 24, 25, 26, and 27) of the lead-in study, PA-ADPKD-303 will serve as the Screening/baseline values for this study. Clinical laboratory assessments completed at Visit 24 of the lead-in study will be used for assessment of eligibility criteria at Visit 1 of this study with the exception of eGFR, which will be determined from the Visit 26 results. Results for other safety assessments including vital signs, pregnancy testing, physical examination and ECG needed for evaluation of eligibility for study PA-ADPKD-304 will be those assessed at Visit 27.

[b] Participants who meet all eligibility criteria for enrollment at Visit 1 will be assigned lixivaptan at a dose of 100 mg BID for 1 week to start the re-titration period. At Visit 2, the dose of lixivaptan will be increased from 100 mg BID to the final dose taken at the end of the PA-ADPKD-303 Maintenance Period for those participants

whose final dose at the end of the lead-in study was greater than 100 mg BID. Participants will continue on the escalated dose for one week before entering the Maintenance Treatment Period. Participants whose final dose in the lead-in study was 100 mg BID (or lower in exceptional cases), will skip Visit 2 and proceed directly to Visit 3/Last Titration Visit and undergo the assessments scheduled for that visit. Dosing will continue for the remainder of the study at this level. However, if there is difficulty with tolerability, the dose may be temporarily reduced. Dosing reductions for participants on Level 2 (100 mg BID) per Table 2 require prior approval from the medical monitor.

[c] During the Follow-up Period, 3 visits will occur to obtain the 3 serum creatinine values for calculation of eGFR. The first visit (V30) will occur on the 8th day (+3 days) after the last dose of lixivaptan treatment and the last visit (V32) will occur on the 28th day (±3 days) after the last dose of lixivaptan treatment. V31 must be scheduled a minimum of 24 hours apart from either V30 or V32 and should occur 12 to 24 days after the last dose of lixivaptan. At the final visit (V32), additional safety and efficacy assessments will be completed as denoted in Table 3.

[d] Visits designated as "Laboratory Only" may be completed at the clinic or remotely by a home healthcare clinician or by a designated third-party that will draw and process samples for shipment to the central laboratory where available and approved.

[e] Visit 2 is a telehealth visit (e.g., telemedicine virtual visit, telephone, or video call (without recording)) with site staff. Visit 2 is only applicable to participants whose final dose in the lead-in study was greater than 100 mg BID. At telehealth Visit 2, lixivaptan treatment compliance will be monitored and lixivaptan reconciliation will occur at Visit 3.

[f] Study Visits are more extensive than laboratory only or telehealth visits. Study Visits designated as "Clinic or Remote Visits" can be performed either on-site or remotely by a Home Health Clinician (HHC). Visits 3, 6, 12, 18, 24 and 27 are designated as "Clinic or Remote Visits". All other Study Visits are Clinic Visits.

[g] Vital signs after the participant has been sitting for 5 minutes include sitting heart rate and sitting blood pressure.

[h] Weight will be measured at Visit 24 (PA-ADPKD-303), Visit 3, Visit 15, Visit 29/ET, and Visit 32. Weight may be measured at any other visit to assess hydration status as necessary.

[i] A brief physical examination will be performed at Visit 1 (Visit 27 of lead-in study), Visit 9, Visit 15, Visit 21, and Visit 32. A full physical examination will be completed at Visit 29/ET. Additional physical examinations will be performed only for assessment of signs or symptoms reported by the participant that might require further evaluation.

[j] Routine pregnancy testing for WOCBP will be performed locally on urine. All positive urine results will be confirmed by a serum pregnancy test at the central lab.

[k] Chemistry blood samples will be collected according to the schedule in Table 3:

- A complete chemistry panel includes the following parameters: albumin; blood urea nitrogen (urea); calcium; chloride; carbon dioxide (CO_2); creatinine, enzymatic; glucose; phosphorous; potassium; protein; sodium; uric acid.
- The liver chemistry panel includes alkaline phosphatase; ALT; AST; bilirubin (total and direct).
- All serum creatinine determinations will be performed by the central laboratory.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice per day
BMI	body mass index
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRO	Contract Research Organization
CS	clinically significant
DILI	drug induced liver injury
DILIN	Drug Induced Liver Injury Network
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
eGFR	estimated glomerular filtration rate
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HERC	Hepatic Events Review Committee
HHC	home healthcare clinician
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
OTC	over-the-counter
PBPK	physiologically based pharmacokinetic
PT	preferred term
QTcF	QT interval corrected for heart rate according to Fridericia's formula

Abbreviation	Definition
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background

Lixivaptan (also known as VPA-985, BIIB030, and CL 347,985) is a potent, non-peptide selective antagonist for the vasopressin V_2 receptor, which is expressed primarily in the collecting duct of the nephron (Chan et al, 1998). Lixivaptan antagonizes the effects of vasopressin that are mediated by the V_2 receptor, resulting in the pharmacologic effect of increased free water excretion, thus decreasing urine osmolality, increasing urine flow, and increasing serum osmolality as well as restoring normal levels of intracellular cyclic adenosine 3',5'-monophosphate (Chebib et al, 2015).

The sponsor (Palladio Biosciences, Inc.) is currently developing lixivaptan for the treatment of autosomal dominant polycystic kidney disease (ADPKD). Lixivaptan had previously been under development for the treatment of symptomatic hypervolemic and euvolemic hyponatremia associated with heart failure and syndrome of inappropriate anti-diuretic hormone secretion.

Additional background information for lixivaptan including an overview of ADPKD and available therapies, the rationale for lixivaptan therapy in ADPKD, summary of non-clinical studies, and summary of clinical studies can be found in the Investigator's Brochure (IB).

1.2 Study Rationale

This is a Phase 3, open-label, roll-over study of the Phase 3 PA-ADPKD-303 trial. It is designed to assess long-term safety of lixivaptan in eligible participants with autosomal dominant polycystic kidney disease (ADPKD) who completed study PA-ADPKD-303: The ALERT STUDY.

ADPKD is the most frequent, inherited cause of end-stage renal failure. Animal models have shown that vasopressin activity is necessary for the disease to manifest and progress. Studies of the vasopressin V_2 receptor antagonist tolvaptan have shown that it can slow the progression of renal function deterioration in patients with ADKD. However, serious drug induced liver injury (DILI) occurs in a certain percentage of patients treated with tolvaptan requiring diligent testing of liver chemistry in all participants and discontinuation of the drug when the test results are elevated in order to prevent serious outcomes. The vasopressin V_2 receptor antagonist, lixivaptan, has also been shown to ameliorate polycystic disease manifestations in animal models of disease. Evidence from Quantitative Systems Toxicology modeling and initial clinical results suggest that lixivaptan does not have the same potential for liver injury. Thus, lixivaptan may represent a safer alternative to tolvaptan with similar efficacy. This Phase 3, roll-over study will enroll completers of study PA-ADPKD-303, an open-label study of lixivaptan in patients who experienced abnormal liver chemistry test results on tolvaptan resulting in permanent discontinuation of tolvaptan and is designed to provide those participants with continued access to lixivaptan as well as allow for the assessment of long-term safety in addition to efficacy of lixivaptan in this population.

Lixivaptan as a safer alternative to tolvaptan

Tolvaptan, a vasopressin V_2 receptor antagonist, has been approved in many territories, to slow the progression of renal function deterioration in patients with autosomal dominant

polycystic kidney disease (ADPKD). However, DILI occurs in a certain percentage of patients taking tolvaptan. Acute liver failure requiring liver transplantation has also been reported (Endo et al, 2019). Patients who are on tolvaptan require frequent testing of liver chemistry and discontinuation of the drug when the test results are elevated in order to prevent serious outcomes.

DILI modeling has allowed for the assessment of potential abnormal liver chemistry tests prior to conducting large clinical trials (Woodhead et al, 2017a). This is a Quantitative Systems Pharmacology model of drug-induced liver injury (DILIsym™). DILIsym integrates physiologically based pharmacokinetic (PBPK) and *in vitro* toxicity data of parent compound and its active metabolites. Specific *in vitro* data incorporated into the model includes drug induced bile acid transporter inhibition, mitochondrial dysfunction, and oxidative stress which has been identified as putative mechanisms for DILI.

DILIsym was employed to model tolvaptan-mediated liver injury (Woodhead et al, 2017b). DILIsym was able to successfully recapitulate the observed toxicity. The frequency of predicted alanine aminotransferase (ALT) elevations, following simulated 90/30 mg split daily dosing, was 7.9% compared with clinical observations of 4.4-5.6% in ADPKD trials. The simulations also demonstrated that the *in vivo* hepatic exposure to tolvaptan and its metabolite, DM-4103, combined with alterations in bile acid disposition and inhibition of mitochondrial respiration were sufficient to account for the initiation of tolvaptan-mediated liver toxicity.

This same platform was used to evaluate the potential of lixivaptan to cause liver toxicity (Woodhead et al, 2020). *In vitro* data relating to reactive oxygen species formation, mitochondrial toxicity, and bile acid transporter inhibition for lixivaptan and its major metabolites (WAY-138451, WAY-141624, and WAY-138758) were collected in parallel with tolvaptan as a positive control. Using these data, lixivaptan and its metabolites were represented in DILIsym. Proposed ADPKD treatment dosing regimens were simulated and the predicted potential for liver enzyme elevations was compared to that previously determined for tolvaptan in DILIsym. Results showed that lixivaptan was not predicted to cause liver enzyme elevations in a simulated human population which included variability in toxicity susceptibility and pharmacokinetics, while tolvaptan was correctly predicted to cause rare liver enzyme elevations in a similar population (Table 4). Additional information regarding the DILIsym evaluation of lixivaptan can be found in the IB.

Table 4. DILIsym simulations of lixivaptan and tolvaptan

Drug	Dose, Duration	Clinical ALT >3 × ULN	Simulated ALT >3 × ULN, n/N
Lixivaptan	200/100 mg q AM/PM, 12 weeks	Study not yet conducted	0/285
Tolvaptan	90/30 mg q AM/PM, 24 weeks	4.4%	18/229 7.86%

Therefore, compared to tolvaptan, *in silico* modeling and simulation have demonstrated that lixivaptan does not have the same potential for liver injury.

A safety assessment of the potential for lixivaptan to be associated with clinical hepatotoxicity in the hyponatremia program was included in the Cardiokine NDA. In the healthy volunteer studies, analysis of adverse events and liver-related laboratory tests showed no evidence of liver toxicity with lixivaptan. In the Phase 2 and Phase 3 trials in participants with hyponatremia, a population prone to liver chemistry abnormalities, there were small mean decreases in ALT, AST, and total bilirubin in the lixivaptan treated participants. Furthermore, there were no instances of hepatotoxicity meeting the definition of Hy's Law among participants treated with lixivaptan. The percentage of participants who had concomitant elevations of ALT >3 × upper limit of normal (ULN) and total bilirubin >2 × ULN was low and numerically lower in the lixivaptan group compared to the placebo group, further suggesting no lixivaptan-related liver toxicity. Analysis of the Phase 2 ADPKD study also did not show any hepatic AEs.

Recently, Palladio has had the opportunity to test the hypothesis of lixivaptan's superior liver safety in a clinical setting. An ADPKD patient who experienced disabling kidney pain was treated with tolvaptan in 2017 with marked clinical improvement. However, tolvaptan-associated liver toxicity manifest as ALT elevation required interruption of tolvaptan treatment. Two subsequent attempts to re-introduce the drug resulted in rapid recurrence of the ALT abnormalities (Figure 2) and the drug was stopped permanently in December 2017. The treating physician reached out to Palladio for access to lixivaptan for treatment of the recurrent disabling pain. Treatment with lixivaptan in this participant was started in 2019 under an expanded access protocol. Pain reduction and improvement in measured quality of life occurred as the dose of lixivaptan was up-titrated. At the time of this writing, there has been no evidence of increased ALT values in this participant after 14 months of therapy with lixivaptan (Figure 3).

Figure 2. Time Course of ALT Levels in Relationship to Dosing of Tolvaptan in a Patient with Painful ADPKD

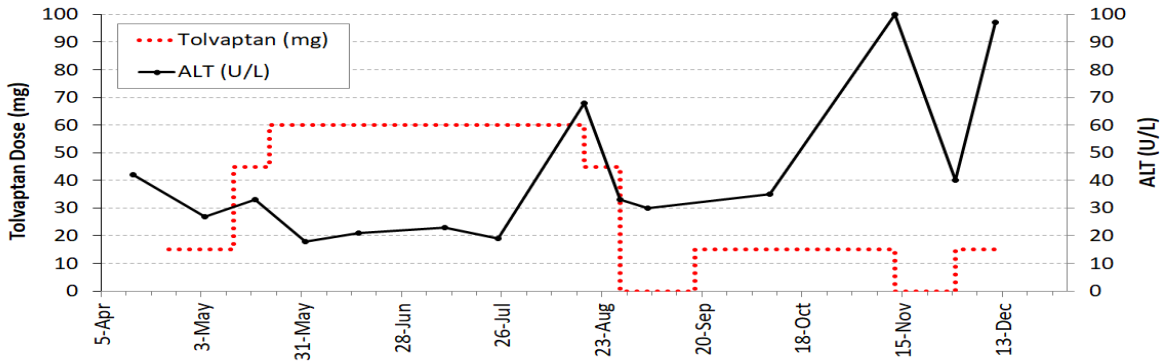
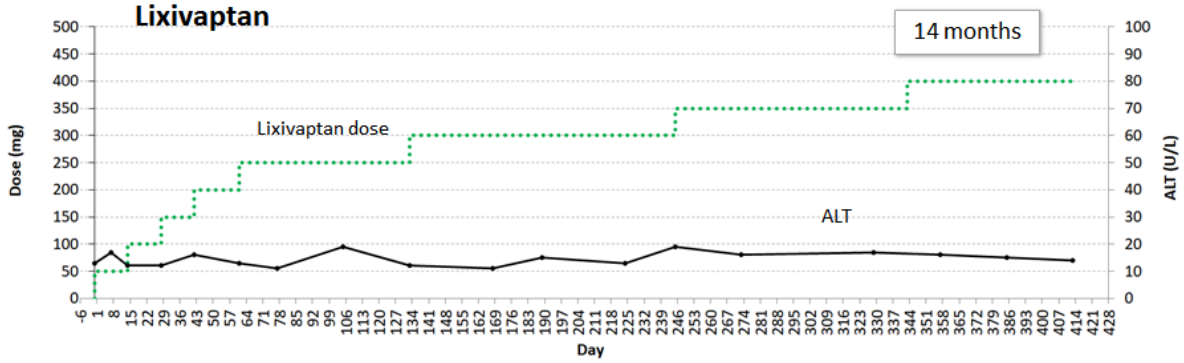


Figure 3. Time Course of ALT Levels in Relationship to Dosing of Lixivaptan in a Patient with Painful ADPKD



These results strongly suggest that lixivaptan may represent a safer alternative to tolvaptan not only for the general patient population, but also for those participants who experienced abnormal liver chemistry test results while receiving tolvaptan. The intent of the PA-ADPKD-303 study is to replicate the experience of hepatic safety with lixivaptan in a larger number of ADPKD patients previously treated with tolvaptan who discontinued the drug permanently because of abnormal liver chemistry test results. This roll-over study (PA-ADPKD-304) will thus provide additional hepatic safety information over a longer treatment experience.

1.3 Dose Rationale

The human equivalent exposure range of lixivaptan to be employed for this study has been shown to be safe and tolerated in nonclinical animal studies and previous clinical studies conducted in healthy participants, in participants with hyponatremia of various etiologies, and in the PA-102 study of patients with ADPKD.

The dose range to be employed for this roll-over study is the same as in the lead-in study PA-ADPKD-303, i.e., 100 mg BID up to 200 mg BID. However, eligible participants completing study PA-ADPKD-303 study will be re-titrated to their final dose from study PA-ADPKD-303 over a 1-to-2-week Re-titration Period in accordance with Table 1.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

- To assess the hepatic safety of lixivaptan with continued dosing.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To characterize the non-hepatic safety and tolerability of lixivaptan
- To assess renal function (efficacy) in participants while on lixivaptan using change in estimated glomerular filtration rate (eGFR).

2.2 Study Endpoints

2.2.1 Primary Endpoint

Safety:

- Proportion of participants with serum ALT levels >3 × ULN during Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent Hepatic Events Review Committee (HERC) to be at least probably related to lixivaptan and resulted in discontinuation of lixivaptan treatment.

2.2.2 Secondary Endpoints

Safety:

- Proportion of participants with serum ALT levels >5 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in discontinuation of lixivaptan treatment.
- Proportion of participants with serum ALT levels >3 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in dose reduction of lixivaptan treatment.
- Safety and tolerability of lixivaptan assessed through evaluation of AEs, clinical laboratory findings (clinical chemistry including additional analyses of liver chemistry tests, hematology, and urinalysis), vital signs and 12-lead electrocardiograms (ECGs).

Efficacy:

- Change in annualized eGFR from baseline (mean of 3 eGFR determinations obtained at Visits 25, 26 and 27 of study PA-ADPKD-303) to final assessment (mean of 3 eGFR determinations obtained during the Follow-up Period).

3 INVESTIGATIONAL PLAN

3.1 Study Design

3.1.1 Overview of Study Design

This is a Phase 3, open-label roll-over study to demonstrate the continued hepatic and non-hepatic safety and renal efficacy of lixivaptan in patients with ADPKD who previously experienced abnormal liver chemistry test results while treated with tolvaptan that resulted in permanent discontinuation of tolvaptan for that reason and subsequently completed study PA-ADPKD-303, the open-label lead in study with lixivaptan. Up to 50 participants can be enrolled and treated with lixivaptan in study PA-ADPKD-303. All participants completing the lead-in study and meeting eligibility criteria for this roll-over study will be able to enroll. It is estimated that approximately up to 40 participants will enroll in this study, assuming 90% of participants complete study PA-ADPKD-303 and 90% meet eligibility and elect to enroll.

There will be a Screening, Re-titration, Maintenance, and Follow-up Period. The Screening Period will be 4 weeks in duration. Assessments completed during the final 4 visits (Visits 24, 25, 26, and 27) of study PA-ADPKD-303 will serve as the screening and baseline assessments for this roll-over study. Visit 27 of the lead-in study will be used as Visit 1 of this roll-over study. Safety assessments performed during Visits 24, 25, 26 and 27 of the lead-in study will also be used for assessment of eligibility and will constitute the baseline values for this study. The mean of the eGFR values obtained at Visits 25, 26, and 27 of the lead-in study will be used to determine the baseline eGFR value for this study. Evaluation of eligibility will be completed at Visit 1 of this study, following signing of the informed consent form (ICF). Participants satisfying all study entry criteria at Visit 1 will be considered enrolled following completion of all Visit 1 study procedures and will be dispensed lixivaptan treatment in accordance with Table 1 to start the Lixivaptan Re-titration Period.

The Re-titration Period will be 1 to 2 weeks. However, Investigators have the flexibility to increase the 2-week period if re-titration needs to go slower or a dose reduction is needed for tolerability or safety reasons. During the 1-to-2-week Lixivaptan Re-titration Period, participants whose final dose during the Maintenance Period of the lead-in study was 100 mg BID will remain on that dose for one week, complete Visit 3 assessments, and then proceed to the Maintenance Treatment Period of the current study with no further up-titration. (**Note:** Eligible participants who completed the lead-in study on 50 mg BID may continue on that dose in this study. Those participants will undergo a one-week re-titration, complete Visit 3 assessments and then proceed to the PA-ADPKD-304 Maintenance Treatment Period). Participants on doses greater than 100 mg BID at the end of the Maintenance Period of study PA-ADPKD-303 will be directly titrated to their final dose of the lead-in study during the second week of the Re-titration Period. Following re-titration, participants will enter the Maintenance Treatment Period. Lixivaptan treatment titration and assignment will be programmed into the Interactive Response Technology (IRT) system.

Participants will then continue on lixivaptan treatment for up to 104 weeks during the Maintenance Treatment Period and will be assessed at a study visit every 12 weeks where

study procedures will include clinical laboratory determinations, including liver chemistry tests. In between quarterly study visits, participants will be required to have blood drawn for liver chemistry determinations every 4 weeks. Where available and approved, visits designated as "laboratory only" may be conducted remotely by a home healthcare clinician (HHC) or by a designated third-party that will process samples for shipment to the central laboratory. Liver chemistry tests may also be drawn at the clinic if that is convenient.

At the end of 104 weeks, lixivaptan treatment will be stopped, and participants will enter the Follow-up Period during which final assessments of safety and efficacy will be obtained over 3 visits starting on the 8th day following the last dose of lixivaptan treatment and continuing through the 28th day.

All assessments and the relative timings are listed in the Schedule of Study Procedures (Table 3). Study procedures by visit are outlined in Section 6. A comprehensive description of study procedures can be found in Section 7. Dosing procedures are outlined in Section 5.

Note that the study or a participant's involvement in the study may be interrupted at any time if safety issues compromise the safety of the participants.

The study schematic is depicted in Figure 1.

3.1.2 Detailed Study Design

Screening Period:

The Screening Period will be 4 weeks in duration. Screening information for assessing eligibility for enrollment will be obtained during the final 4 visits (Visits 24, 25, 26 and 27) of the lead-in study, PA-ADPK-303. Evaluation of eligibility will be initiated following signing of the ICF for this study at Visit 27 of the lead-in study PA-ADPKD-303 which will be Visit 1 of this roll-over study (PA-ADPKD-304). The mean of the eGFR values obtained at Visits 25, 26 and 27 of study PA-ADPKD-303 will be used to determine the baseline eGFR value for this study. Participants satisfying all study entry criteria at Visit 1 will be considered enrolled following completion of all Visit 1 study procedures and will be dispensed lixivaptan treatment in accordance with Table 1 to start the Lixivaptan Re-titration Period.

Lixivaptan Re-titration Period:

Re-titration of lixivaptan in enrolled participants will occur over a 1-to-2-week period. The first week of dosing follows the completion of Visit 1. Participants whose final dose was 100 mg BID at the end of the PA-ADPKD-303 study Maintenance Period will be titrated over one week and then proceed to Visit 3. **NOTE:** Eligible participants whose final dose was 50 mg BID at the end of study PA-ADPKD-303 can continue on that dose in this study, and will also be re-titrated over one week, and then proceed to Visit 3. Following one week of dosing, participants whose final dose at the end of study PA-ADPKD-303 was greater than 100 mg BID, will have their dose of lixivaptan increased from 100 mg BID to the final dose taken at

the end of the Maintenance Period during the second week of the Re-titration Period (see Table 1).

NOTE: Investigators have the option to re-titrate more slowly and/or reduce the dose in the event of emerging tolerability or safety issues. In this instance, the Re-titration Period would be increased as needed.

Maintenance Treatment Period:

Following completion of the Lixivaptan Re-titration Period, participants will continue into the open-label Maintenance Treatment Period following completion of Visit 3 assessments for up to 104 weeks. Participants will be assessed at study visits scheduled every 12 weeks with assessments but will have required liver chemistry testing every 4 weeks at visits designated as "laboratory-only visits". Where available and approved, the laboratory-only visits may be conducted remotely by an HHC or by a designated third-party that will process samples for shipment to the central laboratory. In addition, the liver chemistry tests may be drawn in the clinic if that is more convenient. Furthermore, certain study visits can be performed by an HHC.

Follow-up Period:

Three visits will occur over 4 weeks following the last dose of lixivaptan treatment in order to obtain final assessments. Starting with the 8th day after the last dose of lixivaptan treatment, serum creatinine will be assessed at 3 time points (no less than 24 hours apart between each sampling) over a period of up to 28 days post last dose of lixivaptan. Certain follow-up visits are designated as laboratory-only visits. **NOTE**: If a participant terminates the study early (ET), an eGFR determination from serum creatinine obtained at 3 time points over a period of up to 28 days post last dose, will be carried out.

NOTE: The total duration of participation in this roll-over study from the signing of the ICF at Visit 1 will be approximately 109 to110 weeks.

3.2 Rationale for Study Design

Evidence suggests that lixivaptan may be a safer alternative to tolvaptan with similar efficacy in the treatment of patients with ADPKD. This roll-over study of PA-ADPKD-303 is designed to provide timely, additional supporting evidence of the overall safety, specifically hepatic safety and renal function, of lixivaptan dosing over a 2-year period in these participants.

4 PARTICIPANT SELECTION AND WITHDRAWAL CRITERIA

4.1 Selection of Study Population

Participants completing study PA-ADPKD-303 will be invited to enroll in this study. In this study, up to approximately 40 participants will be enrolled and treated at approximately 25 sites in the US. All participants completing the lead-in study and meeting all the inclusion criteria and none of the exclusion criteria for this study will be eligible to enroll. With the approval of the medical monitor and Investigator, participants who fail inclusion/exclusion criteria due to temporary or correctable reasons may be re-screened up to 2 times after re-consenting each time.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

For entry into the study at Visit 1, each participant must meet the following inclusion criteria:

1. Male or female participants with ADPKD who completed study PA-ADPKD-303
2. Female participants must:
    a. not be pregnant, lactating, or breastfeeding
    b. be either postmenopausal (defined as amenorrhea for ≥12 months), surgically sterile (defined as having undergone hysterectomy and/or bilateral oophorectomy), or if of child-bearing potential (WOCBP) must agree to continue to practice appropriate methods of birth control or remain abstinent (only if this is the usual and preferred lifestyle of the participant) during the full duration of the study and for 30 days after the last dose of lixivaptan treatment. Acceptable forms of contraception include the following:
        - hormonal contraceptives (i.e., oral, intravaginal, transdermal, injectable, implantable)
        - intrauterine device (IUD), including progestin-containing intrauterine devices
        - intrauterine hormone-releasing system (IUS)
        - male sexual partner who has been vasectomized for at least 3 months prior to Screening and who has obtained a follow-up negative sperm count and is the sole sexual partner
        - bilateral tubal ligation
        - Essure® procedure (tubal occlusion)
        - male or female condom with spermicide (cream, spray, gel, suppository, or polymer film)
        - diaphragm, cervical cap, or contraceptive sponge with spermicide

(with or without a male condom)

3. Male participants must agree to continue to use an acceptable form of birth control (see list above) or remain abstinent (only if this is the usual and preferred lifestyle of the participant) during the full duration of the trial and for 30 days after the last dose of lixivaptan treatment.
4. Continued control of hypertension without the use of a diuretic in concert with KDIGO "Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease"
5. Continued adherence to prohibitions on concomitant medications stated in the study PA-ADPKD-303 protocol, and in Section 5.7.1.2 of this protocol, including use of strong or moderate CYP3A4 or CYP2C8 inhibitors or inducers
6. Read, understood, and provided written informed consent after the nature of the study has been fully explained and must be willing to comply with all study requirements and procedures.

4.1.2 Exclusion Criteria

Participants meeting any of the following exclusion criteria at Visit 1 are not eligible for study enrollment:

1. Any contraindication to continued treatment with lixivaptan
2. Clinically significant (CS) incontinence, overactive bladder, or urinary retention (e.g., benign prostatic hyperplasia)
3. New York Heart Association Functional Class 3 or 4 heart failure or other significant cardiac or electrocardiogram (ECG) findings that could pose a safety risk to the participant
4. Hypovolemia on physical examination at Screening
5. The following laboratory results based on serum drawn at Visit 24 of PA-ADPKD-303:
    a. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values >1.5 × upper limit of normal (ULN)
    b. Total bilirubin values >1.5 × ULN
6. eGFR <20 ml/min/1.73 m^2 based on laboratory results from Visit 26 of PA-ADPKD-303
7. A finding at Screening that precludes safe participation in the study or participants who are likely to be non-compliant with study procedures in the opinion of the Investigator or medical monitor.

4.2 Completion and Withdrawal of Participants from the Study

4.2.1 Definition of Completed Participants

A completed treatment participant is one who has completed the procedures beginning with Screening through the last Maintenance Treatment Period visit (Visit 29). A completed study participant is one who has completed the procedures beginning with Screening through the

last Follow-Up Period visit (Visit 32). The end of the study is defined as the last participant's last visit.

4.2.2 Screening Failures

Participants may withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the study site.

During the Screening Period, participants who withdraw their consent or fail to meet all the entry criteria to participate in the study will be designated as "Screen failures". Screen failure participants will be recorded as such on the electronic Case Report Form (eCRF) and do not need to complete an ET Visit or enter the Follow-up Period unless a serious adverse event (SAE) is ongoing, in which case they will be scheduled for Visit 32 in 4 weeks. Screen failure participants who do not meet study entry requirements due to temporary or correctable reasons may be re-screened up to 2 times with the approval of the medical monitor and sponsor.

4.2.3 Participant Withdrawal Criteria

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons.

Participants who discontinue or are discontinued after the Screening Period will be considered as a withdrawal, regardless of whether they have received lixivaptan treatment.

All premature discontinuations and their causes must be carefully documented in the eCRF, and in the AE form (if applicable).

Participants not completing the entire study on lixivaptan treatment should be encouraged to continue with the visit schedule, a modified visit schedule, or telephone follow-up as agreed between the participant and the Investigator. At a minimum, participants should be encouraged to complete the ET Visit (Visit 29) in the clinic within 7 days of lixivaptan treatment discontinuation and the Follow-up Visits (Visits 30 to 32) over the 4 weeks after the last dose of lixivaptan treatment. Participants with ongoing SAEs or AEs believed to be at least possibly related to study medication will continue to be followed until resolution or for 28 days as warranted by the nature of the AE. If the AE is related to abnormal liver chemistry test results, see Section 7.2.7 for additional follow-up requirements.

4.2.4 Reasons for Withdrawal

Reasons for withdrawal (participants who refuse to return for any remaining study visits) or discontinuation (participants who prematurely stop the treatment) at any time during the study may include, but are not limited, to the following:

1. No longer meet the protocol inclusion or exclusion criteria, e.g., require a prohibited concomitant medication.
2. Noncompliance with the protocol.
3. Lack of efficacy.

4. A serious or intolerable AE that, in the Investigator's opinion, requires withdrawal from the study, including but not limited to laboratory safety assessments that reveal CS hematological or biochemical changes from the baseline values, other than changes that are expected for vasopressin antagonists, and symptoms of an intercurrent illness that justifies withdrawal. If the AE is related to abnormal liver chemistry test results, see Section 7.2.7 for additional follow-up requirements. Mild elevations in serum creatinine or serum sodium are known pharmacodynamic effects of vasopressin antagonists like lixivaptan and are transient and reversible. Therefore, participants should not be withdrawn from study participation solely due to mildly elevated serum creatinine or serum sodium. Cases where eGFR has declined by 25% or more from baseline should be discussed with the medical monitor and sponsor.
5. Death.
6. Lost to follow-up.
7. Other (e.g., pregnancy, study burden, development of contraindication to use of lixivaptan treatment).
8. Withdrawal of consent (partial or complete).
9. Investigator's or sponsor's decision to discontinue the participant from the study.
10. Sponsor termination of the study.

Upon occurrence of an SAE or intolerable AE, the Investigator will confer with the medical monitor and sponsor. If a participant is discontinued from lixivaptan treatment because of an AE, the event will be followed until it is resolved or stable or up to 28 days as determined by the Investigator. Any participant may withdraw his or her consent at any time. Participants' safety will be closely monitored throughout the study, and the study will be conducted following Good Clinical Practices (GCP). The entire study may be stopped at any time at the discretion of the sponsor.

4.2.5 Methods to Prevent Loss to Follow-up

The Investigator must make every attempt to follow-up participants who have withdrawn from the study at any time and for any reason. When a participant is "lost to follow-up" (i.e., fails to return for study visits or complete one or more scheduled remote visits), a reasonable effort (3 documented phone calls or 2 phone calls and 2 text messages [if the participant has a mobile phone], on separate occasions, and a follow-up letter sent by registered mail) should be made to contact him/her to determine a reason for the failure to return or complete remote visit(s). If the participant cannot be reached, he/she should be identified as "lost to follow-up" in the eCRF.

4.2.6 Replacements

Participants who withdraw from the study will not be replaced.

4.2.7 Withdrawals Due to Abnormal Liver Chemistry Test Results

Guidance for management of abnormal liver chemistry test results is provided in Section 7.2.7. In some cases, it will be advisable to discontinue lixivaptan treatment and under other circumstances dose reduction might be appropriate. These actions in response to abnormal liver chemistry test results must be discussed with the medical monitor and sponsor prior to taking any action (except in an emergency). If lixivaptan treatment is withdrawn, re-starting lixivaptan should generally be encouraged after discussion with the medical monitor and sponsor, when liver chemistry tests have normalized or stabilized, and in conjunction with a plan for increased frequency of liver chemistry test monitoring. When re-starting lixivaptan treatment after an interruption, the need for re-establishment of dose should be discussed with the medical monitor. In certain circumstances described in Section 7.2.7.2, restarting lixivaptan treatment should only occur when the HERC believes the relationship between the abnormal liver chemistry test results and the lixivaptan treatment is ≤50% according to the DILIN criteria, modified, Section 13.2 (Fontana et al, 2009).

5 LIXIVAPTAN TREATMENT AND CONCOMITANT MEDICATION

5.1 Lixivaptan Treatment

5.1.1 Identity of the Investigational Product

The investigational product, lixivaptan capsule, is formulated as a white, banded, hard gelatin capsule containing 50 mg of lixivaptan, and the inactive ingredients listed in Table 5.

Table 5. Investigational Product

	Lixivaptan
Strength	50 mg
Formulation	Capsules, packaged 30 per bottle
Inactive ingredients	Polyethylene glycol 400, NF/EP; Polyethylene glycol 1000, NF/EP; Povidone (K-17), USP/EP; Polysorbate 80, NF/EP; Butylated hydroxytoluene NF/EP; Butylated hydroxyanisole NF/EP
Manufacturer	PMRS, Inc. 202 Precision Road Horsham, PA 19044
Packager	PCI Pharma Services 4545 Assembly Drive Rockford, IL 61109

5.1.2 Route of Administration

Lixivaptan (capsules) is intended to be taken orally, i.e., to be swallowed whole with water. Lixivaptan can be taken with or without food. The capsule should NOT be opened.

5.1.3 Lixivaptan Packaging, Labeling, and Storage

Lixivaptan capsules will be packaged and labeled by PCI Pharma Services, Rockford, IL, USA according to all local legal requirements and will be labeled in accordance with applicable regulatory requirements.

Lixivaptan should be stored at the study site in its original packaging in a secure, locked area under the responsibility of the Investigator or other authorized individual. At the study site, lixivaptan should be stored in accordance with the specifications detailed in the study pharmacy manual. Once lixivaptan is dispensed, the participant should be instructed to store it in its original packaging and in accordance with lixivaptan treatment labelling at all times until ready to take. For study visits conducted remotely (not applicable to laboratory only visits), study drug will be dispensed and shipped from the study site to the participant's home, or to an alternate location pre-specified by the participant, via an experienced courier approved by the Sponsor. Participants will be provided with written instructions to securely

store the study drug in its original packaging under the conditions described above and not to open the package until the HHC arrives.

5.1.4 Accountability

The Investigator will maintain accurate records of lixivaptan receipt and disposition. In addition, accurate records will be kept regarding when and how much lixivaptan is dispensed and used by each participant in the study. Reasons for departure from the expected dispensing regimen will also be recorded. At the completion of the study, to satisfy regulatory requirements regarding lixivaptan accountability, all unused lixivaptan capsules will be reconciled and returned to the sponsor or designee or destroyed according to applicable regulations and site's applicable Standard Operating Procedures.

5.2 Dose Administered

During all treatment periods, lixivaptan treatment will be administered BID, with the PM dose administered approximately 10 hours after the AM dose.

Lixivaptan will be dispensed following the completion of Visit 1 to initiate the Lixivaptan Re-titration Period in accordance with Table 1. Participants will start the Lixivaptan Re-titration Period at a dose of 100 mg BID, with the exception of those whose final dose in study PA-ADPKD-303 was 50 mg BID. Those participants will initiate re-titration at 50 mg BID and continue on that dose in the current study. Participants whose final dose in the lead-in study was greater than 100 mg BID will be directly titrated to a dose equivalent to their final dose in PA-ADPKD-303 during week 2 of the Re-titration Period.

The most common dosing scenarios are presented in Table 2. With concurrence of the medical monitor, participants may be allowed to enter the Maintenance Treatment Period at a lower dose (50 mg BID) if tolerability is an issue after trying a higher dose during the Re-titration Period.

Throughout the study, participants will continue to adhere to the recommended fluid intake regimen outlined in Section 5.8.

After completing the Re-titration Period (1 to 2 weeks), participants will enter the Maintenance Treatment Period and continue at the lixivaptan dose level achieved at the end of the Re-titration Period. During the Maintenance Treatment Period, the dose may be adjusted downward at the Investigator's discretion if needed to manage non-hepatic side effects and may also be increased back to the dose achieved at the end of the Re-titration Period. The Investigator may temporarily interrupt lixivaptan treatment, if necessary, to manage acute intercurrent illness, tolerability issues, planned or unplanned surgical procedures or life situations, e.g., airplane travel, etc. Participants who require a prolonged interruption due to illness, including COVID-19, or other reasons may be able to restart their lixivaptan treatment when medically stable and following discussion with the medical monitor and sponsor. Re-titration is required in the event of a prolonged interruption (i.e., >4 weeks). Temporary or permanent lixivaptan treatment discontinuation for management of abnormal liver chemistry test results is described further in Section 7.2.7.

5.3 Method of Assigning Participants to Identification Numbers

In the lead-in study (PA-ADPKD-303), each Investigator was assigned a unique 5-digit site number (XXXXX). This site number was concatenated with a leading protocol number (303) and a following 3-digit participant number to assure that each participant was uniquely identified in the clinical database. Thus, a participant number in PA-ADPKD-303 appeared as 303-XXXXX-YYY, i.e., the identification number for the first participant screened at the first site activated in the lead-in study was 303-10001-001.

In this study (PA-ADPKD-304), each participant number will include the 5-digit Investigator site number and the 3-digit participant number assigned in the lead-in study, as well as the current protocol number (304). Thus, a participant identification number in PA-ADPKD-304 will appear as 304-XXXXX-YYY (i.e., if the first participant from site 10001 in PA-ADPKD-303 enrolled in the current study, the identification number would be 304-10001-001).

5.4 Blinding

This will be an open-label study.

5.5 Randomization and Treatment Assignment

This study will not be randomized.

5.6 Treatment Compliance

Dispensing of lixivaptan treatment will be done initially at Visit 1. Subsequently, dispensing of lixivaptan treatment and reconciliation will occur at Visit 3 during the Re-titration Period and every 12 weeks, at clinic or direct-to-participants in advance of remote visits, during the Maintenance Treatment Period. A final reconciliation will be done by the site once each participant completes lixivaptan treatment. Participant compliance will be monitored by capsule counts as lixivaptan treatment is returned.

The dates of all lixivaptan treatment dosing, including interruptions, missed doses or overdose, must be recorded in the eCRF. If the participant is not ≥80% compliant with the prescribed lixivaptan treatment doses during the study, then the period of non-compliance should be noted as significant protocol deviation and the sponsor should be notified. The participant should be re-educated regarding the correct lixivaptan treatment doses to be administered. However, if the Investigator, medical monitor, and sponsor have agreed to a treatment interruption (Section 5.2), then this period of non-compliance will not be considered a protocol deviation.

5.7 Prior and Concomitant Therapy

Participants will be allowed to take their medications to treat chronic conditions unless excluded by this protocol, per Section 5.7.1.2 and provided that their chronic medication therapy meets the conditions outlined in Section 5.7.1.1, including remaining constant throughout the duration of the study (unless there is a documented medical reason to change the dose).

Any concomitant medication deemed necessary for the well-being of the participant during the study may be given at the discretion of the Investigator after consideration of the clinical situation. The Investigator is responsible for ensuring that details regarding concomitant medication use are recorded in the eCRF. For each concomitant medication administered the following details will be documented and recorded in the participant's eCRF: name of medication, dose administered, dates and time of administration, and reason for medication use. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter (OTC) medications. Any changes in concomitant medications will also be recorded in the participant's eCRF.

Upon entering the study, each participant will be instructed about the importance of not taking any medication (including herbal supplements and OTC medications) without consulting the Investigator.

5.7.1.1 Permitted Therapy

Allowed medications include those typically prescribed to treat ADPKD, chronic kidney disease, and their complications such as hypertension. These include angiotensin II receptor blockers (e.g., valsartan, candesartan, telmisartan, irbesartan) and angiotensin-converting enzyme inhibitors (e.g., enalapril, lisinopril). However, certain medications are prohibited, as detailed in Section 5.7.1.2.

Acetaminophen, at doses ≤1 g per day, is permitted for use any time during the study in participants who usually take acetaminophen to control episodic pain. Because of their effect on renal function, use of non-steroidal anti-inflammatory drugs should be minimized.

Non-sedating antihistamines (other than loratadine) and decongestants are permitted on an as-needed basis. Low-dose aspirin (up to 150 mg per day) is permitted.

Chronic use of other concomitant medications that are required to treat a medical condition may be permitted unless otherwise prohibited (see Section 5.7.1.2). Doses of such medications should remain as stable as possible allowing for minor adjustments per the standard of care to treat medical conditions. The stability of certain drugs, such as insulin and warfarin, should be based on the standard of care rather than on a stable dose.

As lixivaptan has the potential to inhibit the metabolism of CYP3A4 and CYP2C8 substrates, care should be exercised when administering lixivaptan in combination with these substrates (Section 5.7.1.2) due to the potential for drug-drug interactions. Caution should be exercised when concomitantly administering simvastatin or amlodipine with lixivaptan. In order to minimize the potential for AEs, the Investigator should consider potential dose adjustments or alternative therapeutic options that are not CYP3A4 or CYP2C8 substrates (e.g., rosuvastatin to replace simvastatin) or that have a high therapeutic index. If participants are receiving simvastatin as background medication and it is not possible to replace simvastatin with rosuvastatin, the dose of simvastatin should be decreased to ≤10 mg daily. If amlodipine is needed for clinical care, the dose should not exceed 5 mg daily.

5.7.1.2 Prohibited Therapy

The following medications are prohibited throughout the study:

- bardoxolone;

- conivaptan;
- demeclocycline;
- diuretics;
- HIF-PH inhibitors;
- metformin (for ADPKD);
- mTOR kinase inhibitors (e.g., everolimus, sirolimus, etc.);
- nicotinamide (for ADPKD);
- SGLT2 inhibitors (e.g., canagliflozin, dapagliflozin, empagliflozin, etc.);
- somatostatin analogs (e.g., lanreotide, pasireotide, octreotide, etc.);
- tolvaptan;
- strong or moderate CYP3A4 or CYP2C8 inducers, including barbiturates, bosentan, carbamazepine, efavirenz, enzalutamide, etravirine, modafinil, mitotane, nevirapine, oxcarbazepine, phenytoin, pioglitazone, rifabutin, rifampin, and St. John's wort;
- strong or moderate CYP3A4 or CYP2C8 inhibitors, including aprepitant, boceprevir, clarithromycin, chloramphenicol (not eye drops), cimetidine, ciprofloxacin, clopidogrel, clotrimazole (if used orally), cobicistat and cobicistat-containing products, crizotinib, cyclosporine, danazol, deferasirox, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, gemfibrozil, HIV protease inhibitors, imatinib, isoniazid, itraconazole, josamycin, ketoconazole, nefazodone, posaconazole, quinupristin/dalfopristin, ritonavir and ritonavir-containing products, telaprevir, teriflunomide, tofisopam, troleandomycin, verapamil, and voriconazole;
- any investigational drug or device;
- medications that may interfere with the accurate measurement of serum creatinine including cimetidine, trimethoprim, pyrimethamine, phenacemide, and aspirin (aspirin dose above 150 mg per day);
- any other drug/treatment including medications, supplements, and herbals with known activity on serum creatinine or interference with serum creatinine assays and/or vasopressin activity or interference with serum creatinine assays and/or vasopressin activity.

5.8 Diet, Fluid, Activity, and Lifestyle Considerations

Restriction of excess dietary sodium and cooked meat protein may prove beneficial to participants with a history of, or predisposition for, hypertension or kidney disease in general. In the absence of alternate regional practices, dietary salt should be restricted to <5g/day and dietary cooked meat protein to <1 g/kg/day. In addition, the amount of meat protein should remain stable from day-to-day, and an increased consumption of meat should not occur the day before scheduled serum creatinine measurements.

Participants will refrain from consumption of grapefruit or Seville oranges (or their juices) from 7 days prior to the first dose of lixivaptan treatment until after the completion of the study.

Increased fluid intake is encouraged in participants with ADPKD. Given the potential for dehydration with lixivaptan treatment, all participants should be instructed to ingest fluids in anticipation of, or at the first sign of, thirst in order to avoid excessive thirst or dehydration. At the initiation of the Re-titration Period, all participants should receive the reminder to ingest at least 3 to 4 quarts (or liters as an approximation of quarts) of fluid (including in

solid, semi-solid, and liquid foods) per day, unless otherwise directed by the Investigator. This recommendation should start at the beginning of the Re-titration Period and continue through the end of the study. Additionally, participants should ingest 1 to 2 cups (approximately 250-500 mL) of water before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia. Dehydration can be monitored by participant self-assessment of symptoms such as lightheadedness or dizziness.

Daily activity including exercise should remain stable during the study and participants should avoid heavy lifting or intense physical exertion on the day before scheduled serum creatinine measurements.

Consumption of alcohol should be limited to 1 alcoholic drink equivalent per day in women and 2 alcoholic drink equivalents per day in men. An alcoholic drink equivalent is 12 ounces (360 ml) of regular beer, or 5 ounces (150 ml) of wine, or 1.5 ounces (45 ml) of distilled spirits.

6 TIMING OF STUDY PROCEDURES

The timing of study procedures is presented in Table 3. Scheduled quarterly visits (except for Visits 9, 15 and 21) may occur in the Investigator's clinic or remotely with an HHC. Visits 9, 15 and 21 must occur in the Investigator's clinic. Other "Laboratory Only" visits at 4-week intervals can be completed remotely by an HHC or by an approved designated third-party.

6.1 Screening Period

The evaluation of both eligibility and baseline values for this roll-over study will be determined from the final 4 visits (Visits 24, 25, 26, and 27) of study, PA-ADPKD-303.

Participants with a signed ICF and meeting study inclusion/exclusion criteria will be considered enrolled into this roll-over study after completion of all Visit 1 study procedures and will begin the Lixivaptan Re-titration Period.

Participants who screen fail due to correctable or temporary reasons may be re-screened at a later time (up to 2 times) with the approval of the medical monitor and sponsor, after new informed consents are obtained.

6.1.1 Visit 1/Visit 27 of PA-ADPKD-303

For participants electing to enroll in this roll-over study, eligibility criteria will be reviewed following the signing of the ICF during Visit 27 of the lead-in study. Visit 27 of study PA-ADPKD-303 will also serve as Visit 1 of this study (PA-ADPKD-304). Assessments performed at earlier visits of the lead-in study that will be utilized to determine eligibility include:

- Visit 24 - laboratory assessments (urinalysis, hematology, complete chemistry, and liver panel)
- Visit 26 - eGFR
- Visit 27 safety assessments (vital signs, pregnancy testing in WOCP, brief physical examination, ECG, AEs, and concomitant medications).

The mean of the eGFR values obtained at Visits 25, 26, and 27 (Follow-up Period) of study PA-ADPKD-303 will constitute the baseline eGFR value for this study. No lixivaptan study treatment will be administered during this time.

After signing the ICF at Visit 1, the following screening procedures will be performed:

- Determine whether the participant is eligible to participate in the study based on meeting all the Inclusion Criteria (Section 4.1.1) and none of the Exclusion Criteria (Section 4.1.2)
    - If the participant is not eligible to participate, the site will record the screen failure in the IRT and complete the appropriate eCRFs. No ET or Follow-up Period visits are needed unless an SAE is ongoing, in which case Visit 32 should be completed.
    - If all study entry criteria are met, contact the IRT to record the participant's completion of Visit 1 and obtain lixivaptan kit number assignments to initiate the Re-titration Period. Participants whose final dose during PA-ADPKD-303 was ≤100 mg BID should receive sufficient lixivaptan for a 7 + 3-day interval in

accordance with Table 2. Participants whose final dose during PA-ADPKD-303 was >100 mg BID, should receive sufficient lixivaptan for a 14 + 3-day interval, including a dose escalation that will begin following completion of Visit 2, in accordance with Table 2. Proceed as follows:

  - Dispense lixivaptan and have participant take the first dose when he/she returns home from the clinic. Instruct the participant to take 2 capsules (100 mg) BID approximately 10 hours apart, e.g., 8 AM and 6 PM. (Instruct participants whose final dose was 50 mg BID during the lead-in study, to take 1 capsule [50 mg] BID)
  - Remind the participant to expect aquaretic effects and to maintain fluid intake to prevent dehydration

- Schedule the participant for Visit 2 to occur in 1 week (**NOTE:** For participants with a final dose of ≤100 mg BID in the lead-in study, omit Visit 2 and schedule Visit 3 in 1 week). Provide the participant with an appointment reminder card and any written instructions.

6.2 Re-titration Period

The Re-titration Period will last from 1 to 2 weeks. Participants will self-administer lixivaptan at home. Participants whose final dose during the Maintenance Period of the lead-in study was ≤100 mg BID will remain on that dose for 1 week and then proceed to Visit 3. Participants on doses greater than 100 mg BID will be directly titrated to their final dose of the lead-in study following completion of the telehealth visit at Visit 2 in the Re-titration period and remain on that dose for 1 week, in accordance with Table 1.

6.2.1.1 Visit 2

Participants whose final dose at the end of the lead-in study was >100 mg BID will have a telehealth visit at Visit 2 of the Re-titration Period.

The following procedures will be performed:

- Check AEs and SAEs
- Assess liver dysfunction (symptoms) in accordance with Part 1 of the checklist and instructions in Appendix 4 (Section 13.4)
- Collect and review concomitant medication information
- Review lixivaptan treatment compliance (capsules to be reconciled during Visit 3)
- Contact the IRT to record the visit
- Instruct the participant to increase his/her dose of lixivaptan based on the dose level guide in Table 2
- Schedule the participant for Visit 3 to occur in 1 week and remind the participant to take adequate fluids. Provide the participant with an appointment reminder card and any written instructions.

Participants whose final dose in the lead-in study was ≤100 mg BID will skip Visit 2 and proceed directly to Visit 3.

6.2.1.2 Visit 3/Last Titration Visit

Participants will either report to the clinic or have a remote visit by an HHC for assessments for the last visit of the Re-titration Period. Dosing will continue for the remainder of the study at the level the participant was receiving at the end of the Maintenance Period of the lead-in study.

If there is difficulty with tolerability, the dose may be temporarily reduced, participant may then enter the Maintenance Treatment Period and the dose will be readdressed at the next clinic visit (Visit 6). Dosing reductions for participants on Level 2 (100 mg BID or less) will require prior approval from the medical monitor.

Participants should bring any remaining lixivaptan treatment into the clinic if having a site visit. If the visit is a remote visit, participant should give any remaining lixivaptan to the HHC.

The following procedures will be performed:

- Check AEs and SAEs
- Assess clinically for liver dysfunction (symptoms and signs) in accordance with the checklist and instructions in Appendix 4 (Section 13.4)
- Collect and review concomitant medication information
- Review lixivaptan treatment compliance/reconciliation
- Check vital signs (sitting blood pressure and heart rate)
- Collect body weight
- Collect urine to conduct a pregnancy test in WOCBP
- Collect blood samples for
    - Complete chemistry panel
    - Liver chemistry panel
    - Hematology
- Contact the IRT to record the visit and obtain lixivaptan kit number assignments for initiation of the Maintenance Treatment Period
- Dispense 12-week supply of lixivaptan and instruct participant on appropriate dosing based on the dose level guide in Table 2
- Schedule the participant for Visit 4 (laboratory only visit) to occur in 4 weeks and remind the participant to take adequate fluids. Provide the participant with an appointment reminder card and any written instructions.

6.3 Maintenance Treatment Period

The Maintenance Treatment Period will last 104 weeks (Visit 4 to Visit 29). Visits designated as “laboratory only” may be completed at the clinic or conducted remotely by an

HHC or by a designated third-party who will draw and process samples for shipment to the central laboratory where available and approved. Laboratory only visits include Visits 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, and 28. Visits 9, 15, 21 and 29 will be completed at the study clinic, while the remaining visits designated as "clinic or remote visits" (Visits 6, 12, 18, 24 and 27) may be performed either on-site or remotely by an HHC.

6.3.1 Visits 4 to 28

Study visits will occur every 12 weeks ± 5 days. Laboratory only visits will occur every 4 weeks ± 5 days on weeks when there is not a clinic or remote visit.

6.3.1.1 Visits 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, and 28/Laboratory Only Visits

The following procedures will be performed for each laboratory only visit:

- Collection of a blood sample for liver chemistry panel
- Site personnel to contact the IRT to register visit
- Site personnel to schedule the participant for the next visit in 4 weeks; confirm where the visit will be performed. Remind the participant to take adequate fluids.

6.3.1.2 Visits 6, 12, 18, 24, and 27/Clinic or Remote Visits

Visits 6, 12, 18, 24 and 27 can be performed either on-site or remotely by an HHC.

The following procedures will be performed at each clinic or remote visit:

- Check AEs and SAEs
- Assess liver dysfunction (signs and symptoms at clinic visits (Part 1 and Part 2 of the checklist); symptoms only at remote visits (Part 1 of the checklist)) in accordance with instructions in Appendix 4 (Section 13.4)
- Collect and review concomitant medication information
- Review lixivaptan treatment compliance/reconciliation
- Check vital signs (sitting blood pressure and heart rate)
- Collect urine to conduct a pregnancy test in WOCBP
- Collect blood samples for
    - Complete chemistry panel
    - Liver chemistry panel
- Contact the IRT at each visit to obtain lixivaptan kit number assignments and complete the visit
- Dispense 12-week supply of lixivaptan and instruct participant to take the appropriate dose BID approximately 10 hours apart, e.g., 8 AM and 6 PM
- Schedule the participant to return in 4 weeks for his/her next laboratory visit (if not already scheduled); confirm where the visit will take place. Also, schedule participant for the next clinic or remote visit in 12 weeks. At each visit, remind the participant to take adequate fluids. Provide the participant with an appointment

reminder card(s) and any written instructions. **Note:** Visit 29 should be scheduled approximately 8 weeks from Visit 27. Dosing instructions should be tailored accordingly.

6.3.1.3 Visits 9, 15, and 21/Clinic Visits

Participants should bring any remaining lixivaptan treatment into the clinic.

The following procedures will be performed at each clinic visit:

- Check AEs and SAEs
- Assess clinically for liver dysfunction (symptoms) in accordance with the checklist and instructions in Appendix 4 (Section 13.4)
- Collect and review concomitant medication information
- Review lixivaptan treatment compliance/reconciliation
- Check vital signs (sitting blood pressure and heart rate)
- Collect body weight (Visit 15 only)
- Perform a brief physical examination
- Perform a 12-lead ECG
- Collect urine to conduct a pregnancy test in WOCBP
- Collect urine for urinalysis (Visit 15 only)
- Collect blood samples for
    - Complete chemistry panel
    - Liver chemistry panel
    - Hematology
- Contact the IRT at each visit to obtain lixivaptan kit number assignments and complete the visit
- Dispense 12-week supply of lixivaptan and instruct participant to take the appropriate dose BID approximately 10 hours apart, e.g., 8 AM and 6 PM
- Schedule the participant to return in 4 weeks for his/her next laboratory visit (if not already scheduled); confirm where the visit will take place. Also, schedule participant for the next clinic or remote visit in 12 weeks. At each visit, remind the participant to take adequate fluids. Provide the participant with an appointment reminder card(s) and any written instructions.

6.3.2 Visit 29/Early Termination

Visit 29 will occur at Week 104 ± 5 days.

Participants will report to the clinic to undergo final Maintenance Treatment Period assessments. These procedures will also be conducted on participants that terminate the study early (Section 6.4.4).

Participants should bring any remaining lixivaptan treatment into the clinic.

The following procedures will be performed:

- Check AEs and SAEs
- Assess clinically for liver dysfunction (symptoms and signs) in accordance with the checklist and instructions in Appendix 4 (Section 13.4)
- Collect and review concomitant medication information
- Review lixivaptan treatment compliance/reconciliation
- Check vital signs (sitting blood pressure and heart rate)
- Collect body weight
- Perform a full physical examination
- Perform a 12-lead ECG
- Collect urine to conduct a pregnancy test in WOCBP
- Collect urine for urinalysis
- Collect blood samples for
    - Complete chemistry panel (including serum creatinine for eGFR)
    - Liver chemistry panel
    - Hematology
- Contact the IRT to register the visit
- Schedule the participant to return for the first follow-up visit (Visit 30) in 8 days + 3 days.

6.4 Follow-up Period

The Follow-up Period will last 28 days and include 3 visits (Visit 30, Visit 31, and Visit 32). Visits 30 and 31 are designated as “laboratory only visits” and may be completed at the clinic or conducted remotely by an HHC or by a designated third-party who will draw and process samples for shipment to the central laboratory where available and approved.

6.4.1 Visit 30

Visit 30 will occur no earlier than 8 (+ 3) days after the last dose of lixivaptan treatment.

The following procedures will be performed at Visit 30 (“laboratory only visit”):

- Collect a blood sample for serum creatinine
- Site personnel to contact the IRT to register visit
- Schedule the participant for the next visit (Visit 31), to occur 12 to 24 (± 3) days after the last dose of lixivaptan treatment.

6.4.2 Visit 31

The following procedures will be performed at Visit 31 (“laboratory only visit”):

- Collect a blood sample for serum creatinine
- Site personnel to contact the IRT to register visit

- Schedule the participant to return to the clinic for Visit 32 to occur 28 (± 3) days after the last dose of lixivaptan treatment.

6.4.3 Visit 32 (End of Study Visit)

Visit 32 is the last visit in this study and will occur 28 (± 3) days after the last dose of lixivaptan treatment. The visit will be conducted in the clinic.

The following procedures will be performed at Visit 32:

- Check AEs and SAEs
- Assess clinically for liver dysfunction (symptoms and signs) in accordance with the checklist and instructions in Appendix 4 (Section 13.4)
- Collect and review concomitant medication information
- Check vital signs (sitting blood pressure and heart rate)
- Collect body weight
- Perform a brief physical examination
- Perform a 12-lead ECG
- Collect urine to conduct a pregnancy test in WOCBP
- Collect urine for urinalysis
- Collect blood samples for
    - Complete chemistry panel
    - Liver chemistry panel
- Contact the IRT to register participant completion in PA-ADPKD-304.

6.4.4 Early Termination Procedures

Participants who terminate the study during the Screening Period will not have an ET visit unless there is an ongoing SAE (see Section 4.2.2).

Participants who terminate the study during the Re-titration or Maintenance Treatment Periods will have ET procedures and follow up procedures performed as described in Section 4.2.3.

7 DESCRIPTION OF STUDY ASSESSMENTS AND PROCEDURES

Before performing any study specific procedures, all potential participants will sign the study ICF. Participants will have the opportunity to have any questions answered before signing the ICFs. The Investigator must address all questions raised by the participant.

The study assessments to be performed at each visit are specified in the study Schedule of Procedures (Table 3).

Visits may occur in the morning or afternoon.

7.1 Efficacy Assessments

7.1.1 eGFR

The eGFR values reported to Investigators from the central laboratory will be calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula from the serum creatinine concentrations taken at Screening and at the visits specified in the Schedule of Procedures (Table 3) when either the complete chemistry panel or serum creatinine is listed. During the Screening Period, serum creatinine assessments from Visits 25, 26, and 27 of study PA-ADPKD-303 will be used to determine the mean eGFR. The mean value will be used as the eGFR baseline. The eGFR assessment at Visit 1 (Visit 27 of the lead-in study) will be carried out on serum creatinine from the complete chemistry sample.

Alteration in the metabolism of creatinine based on changes in meat intake and exercise may impact accuracy of serum creatinine and determination of eGFR. Measures to reduce variability are provided in Section 5.8.

7.2 Safety and Tolerability Assessments

The safety and tolerability of lixivaptan will be assessed by evaluation of AEs, SAEs, physical examinations, vital sign measurements, ECGs, and clinical laboratory parameters (hematology, clinical chemistry including liver chemistry tests, and urinalysis). Additional safety assessments may be performed as needed at the discretion of the Investigator. Safety assessments will be performed at Screening and throughout the study as described in the study Schedule of Procedures (Table 3). Assessment windows are presented Table 3.

7.2.1 Body Height, Weight, and BMI

At Visit 1, body mass index (BMI) will be calculated automatically by the eCRF functionality (BMI [kg/m^2] = body weight [kg] / height^2 [m^2]) using the height recorded in study PA-ADPKD-303 and body weight (pounds or kilograms) measured to the nearest tenth at Screening (Visit 24 of study PA-ADPKD-303). Body weight will subsequently be measured at the timepoints specified in the Schedule of Procedures (Table 3). It is preferable to use the same scale at each visit where body weight is measured, and measurements of height and weight will be without the participant wearing shoes.

7.2.2 Demographics and Medication History

Demographic data (e.g., age, childbearing potential) and medication history will be updated as necessary at Visit 1.

7.2.3 Physical Examinations

A brief physical examination will be performed at Visit 1 (Visit 27 of lead-in study), at designated clinic visits during the Maintenance Treatment Period and at the final visit (Visit 32) in the Follow-up Period (Table 3). A complete physical examination will be conducted at Visit 29/ET. Additional physical examinations will be performed only for assessment of signs or symptoms reported by the participants which may require further evaluation.

Complete physical examinations will include, at a minimum, height and weight, general appearance, and assessment of the following systems: skin, head, ears, eyes, and throat, respiratory system, cardiovascular system, gastrointestinal system, neurologic system, blood and lymphatic systems, and the musculoskeletal system. The physical examination may be performed by the Investigator, a sub-Investigator who is a medical doctor, a qualified nurse practitioner or a physician's assistant in accordance with the site's current practice and local requirements, as applicable.

Brief physical examinations include, at a minimum, weight, and assessment of the following systems: chest and heart auscultation, abdominal examination, neurologic condition (i.e., alert and oriented x3; not including cranial nerves), and edema and hydration assessment. The brief physical examination may be performed by the same individuals who can perform a complete physical examination.

Physical examination findings noted during the Screening will be recorded as AEs as appropriate. New physical examination findings observed after re-initiation of lixivaptan treatment will be classified as being in 1 of 3 categories: normal, abnormal but not clinically significant (NCS), or abnormal and CS. All CS findings will be reported as AEs.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator. Symptom-directed physical examinations will be performed as appropriate for participants experiencing AEs.

7.2.4 Vital Sign Measurements

Vital sign measurements will include systolic blood pressure, diastolic blood pressure, and pulse rate and will be performed at the time-points specified in the study Schedule of Procedures (Table 3). Respiratory rate and body temperature will be measured once at Screening.

Participants will remain at rest in a seated position for a minimum of 5 minutes before vital signs measurements are obtained. For all participants, blood pressure and pulse rate will be measured once at each specified time using an automated sphygmomanometer. Blood pressure measurements will be taken with the appropriate cuff size and in the same arm (whenever possible) for the duration of the study. The arm should be positioned level with the heart and the blood pressure cuff applied directly to the skin (not over clothing). A confirmatory repeat vital sign measurement may be performed at the discretion of the

Investigator. Although sitting is the standard position for measurement of vital signs, a site that uses a different standard of care, e.g., semi-recumbent, may utilize that position as long as all measurements at that site are done in the same position. Other positions to obtain vital signs may be used after discussion with the medical monitor. Any confirmed, clinically significant vital sign measurements must be recorded as an AE. If other procedures are scheduled at the same time point, vital signs should be obtained first, before an ECG and/or blood draw.

7.2.5 12-Lead ECGs

Standard 12-lead ECGs will be performed at the time-points specified in the study Schedule of Procedures (Table 3).

Safety 12-lead ECG intervals will be measured using an ECG machine that automatically calculates the HR and measures PR, QRS, QT and QTcF. The same ECG machine should be used for the same participant throughout the study.

ECGs will be obtained with the participant remaining in a supine or semi-recumbent position following 5 minutes of rest. All ECGs throughout the study for a given participant should be measured in the same position, i.e., either all in a supine position or all in a semi-recumbent position. If other procedures are scheduled at the same time-point, the ECG should be obtained after vital sign measurements and/or before the scheduled blood draw.

For all participants, ECGs will be reviewed, signed, and dated by the Investigator or a qualified designee. The ECGs will be classified as being in one of three categories: normal, abnormal but not clinically significant (NCS), or abnormal and CS. All CS findings will be reported as AEs.

Additional ECGs may be performed if deemed medically appropriate.

7.2.6 Clinical Laboratory Tests

Blood and urine specimens will be collected for the clinical laboratory (hematology, clinical chemistry, and urinalysis) and pregnancy tests (all female participants of child-bearing potential) at the time-points specified in the study Schedule of Procedures (Table 3). Except where noted, all laboratory testing will be performed at the central laboratory, which will return results with normal ranges to the clinical sites. A confirmatory assessment through the central laboratory should be obtained as soon as possible for any CS abnormal laboratory parameter if deemed necessary by the Investigator. Repeat testing for abnormal liver chemistry tests is described in Section 7.2.7.1. Any other repeat laboratory testing for values that are not CS should be discussed first by the Investigator with the medical monitor before such tests are ordered. All routine testing will be conducted in the morning after an overnight fasted state (minimum of 8 hours except for water). Mild elevations in serum creatinine or serum sodium are known pharmacodynamic effects of vasopressin antagonists like lixivaptan, therefore confirmatory assessments for serum creatinine and serum sodium will be at the Investigator's discretion.

Clinical laboratory parameters for analysis are presented in Table 6.

Macroscopic urinalysis will be performed via dipstick. Microscopic examination is needed only if macroscopic results are positive for blood or protein.

Additional liver chemistry tests should be collected if the participant experiences liver chemistry test abnormalities of concern or has suspicious symptoms or signs of liver dysfunction (Section 7.2.7).

Table 6. Clinical Laboratory Parameters

Complete Chemistry Panel	**Hematology**	**Urinalysis**
Albumin	Hematocrit	pH
Blood urea nitrogen (urea)	Hemoglobin	Protein
Calcium	Red blood cell count	Glucose
Chloride	Quantitative platelet count	Ketones
CO_2	WBC count with	Bilirubin
Creatinine, enzymatic*	differential (total and %) only if	Blood
Glucose	WBC count is abnormal:	Urobilinogen
Phosphorous	Neutrophils	Leukocytes
Potassium	Lymphocytes	Nitrite
Protein	Monocytes	Microscopic examination
Sodium	Eosinophils	(if positive for
Uric Acid	Basophils	blood, protein,
		nitrite, or
		leukocytes)
Serum Creatinine*		
Creatinine, enzymatic		
Liver Chemistry Panel	**Other Tests**	
Alanine aminotransferase	Urine or serum pregnancy test	
Alkaline phosphatase	(WOCBP only)	
Aspartate aminotransferase		
Bilirubin Total and Direct		

Abbreviations: CO_2 = carbon dioxide; WBC = white blood cell; WOCBP = women of childbearing potential

*serum creatinine will be assessed as part of the complete chemistry panel at study visits where a complete chemistry panel is required (Table 3)

7.2.6.1 Sample Collections

Instructions regarding the collection, processing, and shipment of laboratory samples are detailed in a separate laboratory manual. All samples will be given a unique identifier. The sample collection date and time will be entered into the eCRF.

7.2.7 Assessment of Liver Symptoms, Signs, or Test Abnormalities

Testing for hepatic transaminases (ALT/AST), alkaline phosphatase, and total and direct bilirubin will be performed at the time-points specified in the Schedule of Procedures (Table 3). Management of hepatic and liver chemistry test abnormalities is discussed below.

The appearance of any suspicious symptoms or signs of liver dysfunction as described in Appendix 4 (Section 13.4) in a participant at any time during the study should trigger prompt testing of liver chemistry tests (i.e., within 48 hours).

7.2.7.1 Requirements for Additional Liver Chemistry Testing

To determine when repeat liver chemistry testing is necessary, follow the instructions in Table 7.

Table 7. Additional Liver Chemistry Testing and Other Testing

Participants with Liver Chemistry Values Exceeding Eligibility Requirements at Screening	Participants with Eligible Liver Chemistry Values at Screening
Participants with transaminase (ALT/AST) or total bilirubin values above the values in the exclusion criteria (>1.5 × ULN) during the Screening Period will not proceed further in the study. Any required follow up should be part of routine clinical care. However, if evaluation indicates a reversible cause of liver disease, such participants may be re-screened in consultation with the medical monitor and sponsor when such liver chemistry test results return to values allowing entry into the study.	Any transaminase value >3 × ULN or total bilirubin >2 × ULN during the Re-titration or Maintenance Treatment Periods requires immediate retesting within 48 hours. Local laboratory testing is acceptable with collection of a concurrent central laboratory sample for confirmation whenever possible. During the time that values remain elevated, testing should be done at least weekly for the first month, gradually returning to monthly as indicated by the results. Individual cases that either resolve quicker or slower should be discussed with the medical monitor and sponsor. The medical monitor will discuss with the Investigator any additional laboratory testing or imaging depending on the case circumstances. Examples of such testing are shown in Appendix 3 (Section 13.3).

7.2.7.2 Changes in Lixivaptan Dosing if Liver Chemistry Test Abnormalities Occur During the Titration or Maintenance Treatment Periods

After the Investigator consults with the medical monitor and sponsor, temporary reduction in dose or interruption of lixivaptan treatment administration must be instituted if liver

transaminase levels >3 × ULN or total bilirubin levels >2 × ULN are observed during the Re-titration or Maintenance Treatment Periods. All elevations meeting these thresholds will be assessed by the HERC. In the case of lixivaptan treatment interruption, re-starting lixivaptan treatment should be encouraged (see exception below) after discussion with the medical monitor and sponsor, when liver chemistry tests have normalized or stabilized, and in conjunction with a plan for increased frequency of liver chemistry test monitoring.

In the presence of such liver chemistry test abnormalities, additional clinical testing (examples listed in Appendix 3 (Section 13.3) may be recommended by the medical monitor and sponsor and those results reported according to local guidelines.

Treatment with study drug cannot be resumed in participants when:

- transaminase levels >8 × ULN at any time,
- transaminase levels >5 × ULN for more than 2 weeks, or
- concurrent elevations of transaminase levels >3 × ULN **and** total bilirubin >2 × ULN

except under these circumstances:

> Participants with these levels of abnormality may be re-challenged with lixivaptan treatment if abnormalities were adjudicated as having a ≤50% likelihood of being related to lixivaptan treatment (per DILI Network [DILIN] probability criteria, modified), Appendix 2 (Section 13.2) (Fontana et al, 2009) by the HERC, and the Investigator, medical monitor, and sponsor agree to an intensive monitoring plan to mitigate risk. The participant must also be willing to comply with these monitoring measures, be informed of the potential risks, and consent to lixivaptan treatment re-challenge.

Liver chemistry test increases of a lesser extent should be discussed with the medical monitor. They may be related to the underlying variability of such tests in ADPKD participants. Generally, dosing should continue, but the frequency of laboratory testing should increase, particularly during the Maintenance Treatment Period. Slowing of re-titration may also be considered if the abnormalities occur during the Re-titration Period.

7.2.7.3 Special Reporting of Liver Events

A liver dysfunction details eCRF will be utilized during the study. The type of information needed to complete it is provided in Appendix 4 (Section 13.4). The purpose of the liver dysfunction details eCRF and additional testing is to facilitate review of each participant who develops liver chemistry test abnormalities and/or signs or symptoms of liver dysfunction during the study to determine the probable cause(s) of these abnormalities. The review will be performed by an independent HERC using DILIN probability criteria, modified (0 to 5% = unrelated; 6 to 25% = unlikely, 25% to 50% = possibly, 51% to 75% = probably, 76% to 95% = very likely, >95% = definite) (Fontana et al, 2009). The HERC will independently decide attribution and will communicate in writing with the sponsor. The results of the HERC review will be used in assessing the primary and secondary endpoints. The result of these analyses may be presented separately from the final clinical study report (CSR).

The Investigator must complete the liver dysfunction details eCRF and submit it within 24 hours of awareness through the SAE reporting pathway (described in Section 7.2.8.3) for any

participant who develops an Adverse Event of Special Interest (AESI) related to abnormal liver chemistry test results or clinical signs or symptoms. Specifically, any participant who

- develops any signs or symptoms of hepatic dysfunction (see Appendix 4 [Section 13.4])
- discontinues treatment due to a liver-related AE,
- reports a serious liver-related AE,
- develops ALT or AST levels >3 × ULN,
- develops total bilirubin levels >2 × ULN.

The AESI report form should be updated as new information becomes available.

7.2.8 Adverse Events

7.2.8.1 Definitions of Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to lixivaptan treatment or their clinical significance, as outlined in Section 7.2.8.2 below.

An AE is defined as any untoward medical occurrence in a participant enrolled into this study regardless of its causal relationship to lixivaptan treatment.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to lixivaptan treatment in this study or any event already present at baseline that worsens in either intensity or frequency after exposure to lixivaptan treatment.

An SAE is defined as any event that results in death, is immediately life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Hospitalization does not include admissions for treatment of a pre-existing condition, including surgery, not associated with a new AE; respite care; social reasons; administrative reasons; skilled nursing care; rehabilitation; hospice; or same-day surgery.

7.2.8.2 Eliciting and Documenting Adverse Events and Serious Adverse Events

All AEs and SAEs will be recorded from the time the ICF is signed until study completion.

At every study visit, participants will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to participant observations, any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital sign measurements, physical examination findings), including those that worsen from baseline, deemed to be CS in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

7.2.8.3 Reporting Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes lixivaptan treatment, dose, event term, date of onset, Investigator-specified assessment of severity and relationship to lixivaptan treatment, date of resolution of the event, seriousness, any required treatment or evaluations, and outcome. AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time the participant is screened for eligibility, i.e., medical history, but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

However, any safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition, are not to be reported as AEs or SAEs.

For the purpose of this study, liver events are considered to be AESIs. Liver events will be reported directly from the electronic data capture [EDC] system.

Pregnancy events will need to be reported on special pregnancy forms to ICON PVSS.

Any AE that meets SAE or AESI criteria will be reported to ICON Pharmacovigilance & Safety Services (PVSS) immediately (i.e., within 24 hours) after site personnel first learn about the event. Investigators should record all SAE/AESI details available, including Investigator causality assessment, on the AE eCRF or appropriate AESI form and submit the report via the electronic data capture (EDC) system within 24 hours of becoming aware of the event. Notification of SAE/AESI entry will be generated and sent to ICON PVSS via the EDC system. Pregnancy events will also be reported to ICON PVSS within 24 hours of recognition of the event, but on the special forms provided.

In the event the EDC system is unavailable, a completed SAE Report Form should be submitted to ICON PVSS as an email attachment or by fax to the email address / fax number below. The EDC system must be updated with the information on the paper report as soon as the EDC is available. The preferred method of reporting on paper is via email:

ICON PVSS Email Address: ICON-Safety-CentralReceipt@iconplc.com

or via fax to:

ICON PVSS Fax: 1-215-616-3096 (within US)

ICON PVSS Fax: +44 (0)208 100 5005 (outside US)

Should the site have questions or concerns regarding SAE report submission, the site may elect to call the ICON PVSS SAE Hotline number. The site will be asked to provide the following information: protocol number, site number, participant identifiers, event term, lixivaptan treatment information, relationship of the event to lixivaptan treatment.

- ICON PVSS SAE Hotline Number: +1-888-426-8801 (within US) – Toll Free Number or +1-281-295-4889 (outside of US)

In a study-related health emergency, for discussion of urgent protocol medical-related questions when the assigned medical monitor for a study cannot be reached, an on-call physician can be reached 24 hours per day, 7 days per week via an ICON Call-Center:

- Telephone: +1 857-957-5013
  (a chargeable telephone number allowing a global reach from both landlines and mobile phones)
- https://icophone.iconplc.com/24-7-Medical.pdf (list of country-specific toll-free telephone numbers).

7.2.8.4 Assessment of Severity

AEs should be graded as mild, moderate, or severe, using the following definitions:

- Mild: Awareness of signs or symptoms, but easily tolerated and of a minor irritant type, causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent do not require documentation of onset and duration of each episode.

7.2.8.5 Assessment of Causality

The Investigator's assessment of causality must be provided for all AEs. The causality is the determination of whether there exists a reasonable possibility that the lixivaptan treatment itself caused or contributed to an AE.

If the final determination of causality is unknown and the Investigator does not know whether the lixivaptan treatment caused the event, then the event will be handled as "possibly related to lixivaptan treatment" for reporting purposes. If the Investigator's causality is "unknown, but not related to lixivaptan treatment", this should be clearly documented on study records.

The relationship of an AE to the administration of lixivaptan treatment will be assessed and recorded on the eCRF. Terms used to describe the degree of causality between lixivaptan treatment and an AE are: definitely, probably, possibly, unlikely, or not related. The best

estimate at the time of reporting of the causal relationship between the experimental intervention and an AE and the degree of certainty about causality will be graded using the criteria specified in Table 8.

Table 8. Guideline for Assessment of Adverse Event Causality

Relationship to Lixivaptan Treatment	Description
Not Related	The AE is clearly due to extraneous causes (e.g., underlying disease, environment) or exposure to the investigational product has not occurred. Such events MUST have an alternative, definitive etiology documented in the participant's medical record.
Unlikely Related	A potential relationship between lixivaptan treatment and the AE could exist (i.e., the possibility cannot be excluded), but the AE is most likely explained by causes other than the lixivaptan treatment (e.g., could readily have been produced by the participant's clinical state or could have been due to environmental or other interventions).
Possibly Related	The AE and administration of lixivaptan treatment are reasonably related in time and/or follow a known pattern of response, and the AE can be explained equally well by causes other than lixivaptan treatment (e.g., could readily have been produced by the participant's clinical state or could have been due to environmental or other interventions).
Probably Related	The AE and administration of lixivaptan treatment are reasonably related in time and/or follow a known pattern of response, and the AE is more likely explained by lixivaptan treatment than other causes.
Definitely Related	The AE and administration of lixivaptan treatment are related in time, and a direct association can be demonstrated (e.g., disappears or decreases with reduction in dose or cessation of lixivaptan treatment/investigational product and recurs with re-exposure).

7.2.8.6 Follow-Up of Participants Reporting Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed to satisfactory resolution, until the Investigator deems the event to be chronic or not CS, or until the participant is considered to be stable.

7.2.8.7 Overdose Management

An overdose is any dose of lixivaptan treatment given to a participant or taken by a participant that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the Investigator and also reported to the sponsor. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF. In the event of suspected overdose, the appropriate supportive clinical care including fluid replacement should be instituted at the discretion of the Investigator or as dictated by the participant's clinical status.

7.2.8.8 Pregnancy

Pregnancy is not regarded as an AE unless there is a medical/surgical complication. Any pregnancy of a participant or the partner of a participant that occurs during study participation must be reported using a clinical study pregnancy reporting form. To ensure participant safety, each pregnancy must be reported through this mechanism to ICON PVSS within 24 hours of learning of its occurrence.

The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the participant was discontinued from the study. Pregnancy complications and terminations of pregnancy will be reported as an SAE if SAE criteria are fulfilled. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the participant has completed the study, and considered by the Investigator as possibly related to the study treatment, must be promptly reported to ICON PVSS.

7.2.9 Clinical Laboratory and Other Safety Assessments

Any abnormal clinical laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital sign measurements), including those that worsen from baseline, felt to be CS in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

However, any safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition, are not to be reported as AEs or SAEs.

7.2.10 Hepatic Events Review Committee (HERC)

The HERC consists of 4 expert hepatologists who will review demographic, medical and medication history, safety data and any other relevant data as available on participants who develop liver abnormalities of concern during the study.

This committee will independently determine the probable causality for instances of suspected liver dysfunction and liver chemistry test abnormalities of concern (Section 7.2.7) and of relatedness to lixivaptan.

The results of these reviews will be captured on an eCRF and used for analysis of the primary and secondary safety endpoints. A full report may be provided separately from the clinical study report.

8 STATISTICAL AND ANALYTICAL PLAN

The statistical and analytical plan for this clinical study is summarized below. Further details are provided separately in the Statistical Analysis Plan (SAP).

8.1 Sample Size

All participants in the lead-in study (PA-ADPKD-303) who satisfy all eligibility criteria and sign the Informed Consent may be enrolled into this roll-over study. It is estimated that approximately 40 participants will be able to enroll assuming approximately 90% of participants complete the lead-in study and 90% of those meet all eligibility criteria and elect to enroll in this roll-over study.

NOTE: Up to 50 participants were to be enrolled and treated in the lead-in study (PA-ADPKD-303).

8.2 Populations for Analysis

The following populations will be used for analyzing the data:

Enrolled Population: The Enrolled Population is defined as all participants who meet all eligibility criteria during the Screening Period and complete Visit 1. All general summaries, except safety and efficacy analyses are based on the Enrolled Population, unless specified otherwise.

Safety Population: The Safety Population is a subset of the Enrolled Population defined as those participants who received at least 1 dose of lixivaptan. This population will be utilized for all safety analyses.

Efficacy Population: The Efficacy Population is a subset of the Safety Population defined as those participants who have at least 1 eGFR determination during the Screening Period (Follow-up Period of study PA-ADPKD-303) and have at least 1 eGFR determination during the Follow-up Period. This population will be used for all efficacy analyses.

8.3 Analysis of Demographic and Baseline Characteristics

Descriptive statistics for demographic (e.g., age, race, and sex) and baseline (e.g., eGFR) characteristics will be presented for the Enrolled, Safety and Efficacy Populations.

8.4 Safety Analyses

8.4.1 Primary Hepatic Safety Analysis

Descriptive statistics (n, percentage and 95% confidence intervals) will be used to present the proportion of participants with serum ALT levels >3 × ULN that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in discontinuation of lixivaptan treatment during the Lixivaptan Re-titration or Maintenance Treatment Periods.

8.4.2 Secondary Hepatic Safety Analyses

Similarly, descriptive statistics (n, percentage and 95% confidence intervals) will be utilized to present the 2 secondary endpoints: 1) the proportion of participants with serum ALT levels >5 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were

assessed by the independent HERC to be at least probably related to lixivaptan and resulted in the discontinuation of lixivaptan treatment; and 2) the proportion of participants with serum ALT levels >3 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in lixivaptan dose reduction

8.4.3 Additional Hepatic Safety Analyses

The proportion of participants who develop any of the following abnormalities during the Lixivaptan Re-titration or Maintenance Treatment Periods will be tabulated and presented descriptively:

- >3 ×, 5 ×, 10 ×, and 20 × ULN elevations for ALT
- >3 ×, 5 ×, 10 ×, and 20 × ULN elevations for AST
- >3 ×, 5 ×, 10 ×, and 20 × ULN elevations for either ALT or AST
- ALT or AST levels >2 × their baseline
- Any elevation of total bilirubin >2 × ULN
- Any elevation of alkaline phosphatase >2 × ULN
- Elevation of aminotransferase (>3 × ULN) accompanied by elevated bilirubin (>2 × ULN) and displayed as evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots
- Elevation of aminotransferase in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue
- Possible liver-related deaths and liver-related treatment discontinuations.

8.4.4 Non-hepatic Safety Analyses: Adverse Events

The number and percentage of participants and the number of events during the Re-titration and Maintenance Treatment Periods will be presented for TEAEs, SAEs, treatment-related TEAEs, and TEAEs leading to premature withdrawal according to the system organ class (SOC) and preferred term (PT) assigned to the event using MedDRA. In addition, TEAEs will also be summarized by SOC, and PT separately by maximum severity and relationship to lixivaptan treatment. Listings of deaths and serious TEAEs will be provided. Similarly, number and percentage of participants will be presented for TEAEs, SAEs, and treatment-related TEAEs during the Follow-Up Period.

All AE data will be listed for all participants. Both the Investigator's verbatim terms and the MedDRA preferred terms will be listed for each participant. Listings will also include the SAEs, start and end time and date of AEs, relationship to lixivaptan treatment, severity, and action taken for the AEs. Adverse events with a relationship to lixivaptan treatment considered possibly, probably, or definitely related will be considered related.

8.4.5 Clinical Laboratory Tests

Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) for clinical laboratory data and changes from baseline will be presented for each scheduled time point.

The Baseline value is the last value observed prior to first administration of lixivaptan treatment and any information taken after first administration of lixivaptan treatment is regarded as post-baseline information. The change-from-baseline variables will be calculated as the postbaseline value minus the value at baseline. Change from baseline on continuous data will be summarized using descriptive statistics at each scheduled time point. For categorical data, change from baseline will be summarized using frequency and percentage at each scheduled time-point.

Individual data listings of clinical laboratory results will be presented for each participant. Values outside of the clinical laboratory's reference range (i.e., those with low or high values) will be flagged in the clinical laboratory listings.

For all continuous clinical laboratory variables, a shift table comparing the baseline value (normal, low, and high) to last observation on treatment will be presented.

For urinalysis, a shift table comparing the baseline value to the maximum value will be presented (using number of participants with results of negative, trace, or positive).

8.4.6 ECGs

Observed values and changes from baseline for continuous ECG parameters including heart rate, ventricular rate, PR interval, QRS duration, QT interval (uncorrected), and QTcF interval will be summarized over each scheduled time-point in terms of absolute values using descriptive statistics (n, mean, SD, median, minimum, and maximum). In addition, a summary shift table comparing baseline interpretation (normal, abnormal - NCS, abnormal - CS) to the Investigator interpretation at each time point will also be presented.

A listing will be provided for Investigator-identified ECG abnormalities from safety ECGs. Overall evaluation of safety ECGs will be summarized using frequency counts and percentage of participants as normal or abnormal, and the relevance of the abnormality will be summarized by CS or NCS.

8.4.7 Vital Signs

Changes from baseline in vital signs at each scheduled time-point will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). The baseline value is defined as the last value observed prior to first administration of lixivaptan treatment. The change from baseline is defined as the postbaseline value minus the baseline value.

8.5 Efficacy Analysis

Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented for observed values at baseline and end of study (Follow-up Period), as well as the annualized change from baseline in eGFR at the end of the study (Follow-up Period). Baseline eGFR is defined as the mean of the 3 eGFR assessments obtained during the Screening Period (Visits 25, 26, and 27 of study PA-ADPKD-303). However, if any values are missing, the remaining values will be used to determine the baseline eGFR. The endpoint eGFR is defined as the mean of 3 eGFR assessments obtained during the Follow-up Period of this study. However, if any values are missing, the remaining values will be used to determine the endpoint eGFR. To compensate for the effect of subjects prematurely discontinuing from treatment, the changes from baseline will be annualized by multiplying each participant’s change from

baseline by 365.25 days divided by the duration from the median of the baseline eGFR assessments to the median of the 3 eGFR assessments made during the post-treatment, follow-up assessments in days.

8.6 Statistical Analysis Methodology

Statistical analysis will be performed using SAS® software Version 9.4 or higher. All continuous variables will be summarized using the following descriptive statistics: number of non-missing observations (n), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using the following descriptive statistics: frequency counts and percentages and 95% confidence intervals for the primary and secondary safety endpoints. All data will be listed in data listings.

Further details of the statistical analyses, methods, and data conventions are described in the SAP. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate in the plan.

8.7 Data Quality Assurance

Standard operating procedures are available for all activities performed at the study sites relevant to the quality of this study. Designated study site personnel will be responsible for maintaining quality assurance and quality control to ensure that the study conduct as well as data collection and documentation are performed in compliance with the study protocol, GCP requirements, and applicable regulatory requirements.

All clinical data will undergo source document verification by the Clinical Research Associate (CRA) and data review by Data Management prior to database lock. Programmed edit checks are also implemented to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock. Electronic CRFs can be printed directly from the database. Each eCRF will be reviewed and signed electronically by the Investigator.

8.7.1 Data Management

An eCRF is required and should be completed for each included participant. The completed original eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of the sponsor or appropriate regulatory authorities, without written permission from the sponsor.

As part of the responsibilities assumed in conducting the study, the Investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the eCRFs and any other data collection forms. The eCRFs must be signed by the Investigator to attest that the data contained on the eCRFs are true. Any corrections to entries made on the eCRFs must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's participant chart. In

these cases, data collected on the eCRFs must match the data in those charts.

In some cases, the eCRF, or part of the eCRF, may also serve as source documents. In these cases, a document should be available at the Investigator's site as well as at the sponsor and clearly identify those data that will be recorded on the eCRF, and for which the eCRF will stand as the source document.

The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECGs, etc.

Investigative site personnel will enter participant data into eCRFs using the EDC system designated by the sponsor. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data) and follow Clinical Data Interchange Standards Consortium (CDISC) standards.

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures of the contract research organization (CRO) to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using the MedDRA and World Health Organization Drug Dictionaries, respectively.

After database lock, each study site will receive all site-specific eCRF data for the study, including full discrepancy and audit history. Additionally, a copy of all the study site's data from the study will be created and sent to the sponsor for storage. The CRO will maintain a duplicate copy for their records. In all cases, participant's initials will not be collected or transmitted to the sponsor.

9 ETHICS

9.1 Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, ICFs, and other relevant documents, e.g., written participant instructions, recruitment advertisements, if applicable, from the Institutional Review Board/Ethics Committee (IRB)/(EC) before involvement of human participants in research studies. All correspondence with the IRB/EC should be retained in the Investigator Site File. Copies of IRB/EC approvals should be forwarded to the sponsor.

All IRB/EC approvals should be signed by the IRB/EC chairperson or designee and must identify the IRB/EC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/EC. The Investigator must promptly supply the sponsor or its designee, the IRB/EC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and all applicable regulations. In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation (ICH) tripartite guideline E6 (R2), GCP, and applicable local regulatory requirements and laws.

9.3 Participant Information and Consent

Written informed consents in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each participant before entering the study, upon re-screening, and when performing any unusual or non-routine procedure that involves risk to the participant. Informed consent templates may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consents should be reviewed by the sponsor or its designee or both before IRB/EC submission. Once reviewed, the consents will be submitted by the Investigator to his or her IRB/EC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participants must sign the revised form.

Before recruitment and enrollment, each prospective participant or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the participant /legal guardian understands the implications of participating in the study, the participant / legal guardian will be asked to give consent to participate in the study by signing the ICF.

The Investigator shall retain the signed original ICF(s) and give a copy of the signed original

form to the participant or legal guardian.

10 INVESTIGATOR'S OBLIGATIONS AND STUDY PERSONNEL

The study will be conducted by qualified Investigators under the sponsorship of Palladio Biosciences, Inc. (the sponsor).

The contact information for the sponsor's Chief Medical Officer and the CRO's medical monitor are listed on the cover page of this protocol. Contact information for other sponsor personnel, ICON Clinical Research Limited, the designated CRO, and other vendors are listed in the Investigator Site File provided to each site.

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participants' confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without participants' (or legal guardians') written permission, except as necessary for monitoring and auditing by the sponsor, its designee, the Food and Drug Administration (FDA), or the IRB/EC.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor sponsor's representatives is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor sponsor's representatives is financially responsible for further treatment of the participant's disease.

10.3 Investigator Documentation

Before beginning the study, the Investigator will be asked to comply with ICH E6 (R2) Section 10.4 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/EC written approval and any other local approval, as appropriate
- Original signed Investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the Investigator and each Sub-Investigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/EC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the participant or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

10.4 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6 (R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of participants begins.

10.5 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 (R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the study site IRB as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority with any reports required.

10.8 Records Retention

To enable evaluations and/or audits from regulatory authorities or the sponsor, the Investigator agrees to keep records, including the identity of all participants (sufficient

information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the sponsor, such as another Investigator, another institution, or to the sponsor. The Investigator must obtain the sponsor's written permission before disposing of any records, even if retention requirements have been met.

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

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 STUDY MANAGEMENT

11.1 Monitoring

11.1.1 Monitoring of the Study

The CRA and/or designee, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the CRA will visit the Investigator and study site at periodic intervals, or conduct central or remote monitoring, in addition to maintaining necessary telephone, email and letter contact. The CRA will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.2 Inspection of Records and Quality Assurance

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/EC review, and regulatory inspections by providing direct access to all study records. In the event of an audit or inspection, the Investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (e.g., FDA or other regulatory agency) access to all study records.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits, or inspections and that sufficient time is devoted to the process.

The Investigator should promptly notify the sponsor and/or its designee of any inspections scheduled by any regulatory authorities and promptly forward copies of any related reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the Investigator's IRB/EC for approval before participant can be enrolled into an amended protocol, and before the changes can be implemented.

11.2.2 Protocol Deviations

The Investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study participants without prior IRB/EC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol

amendments should be submitted to the IRB/EC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is defined as an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the Investigator. A major deviation occurs when there is not adherence to the protocol by the participant or Investigator that results in a significant, additional risk to the participant. Major deviations can include not adhering to inclusion or exclusion criteria, enrollment of the participant without prior sponsor approval, or not adhering to FDA regulations or ICH GCP guidelines, and may lead to the participant being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the Clinical Monitor throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of deviations. The IRB/EC should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Although the sponsor has every intention of completing the study, the sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the final end of study assessment.

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the CSR is prepared and provided to the regulatory agency as required by the applicable regulatory requirement(s). The sponsor will also ensure that the CSR in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and content of CSRs.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the CSR, the sponsor will provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate. The study results will be posted on publicly available clinical trial registers.

12 REFERENCE LIST

1. Chan PS, Coupet J, Park HC, Lai F, Hartupee, D, Cervoni P, Dusza JP, Albright JD, Ru X, Mazandarani H, Tanikella T, Shepherd C, Ochalski L, Bailey T, Lock YYW, Ning X, Taylor JR, Spinelli W. 1998. VPA-985, a nonpeptide orally active and selective vasopressin V_2 receptor antagonist. Adv Exp Med Biol. 449:439-443.
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3. Endo M, Katayama K, Matsuo H, et al. 2019. Role of liver transplantation in tolvaptan-associated acute liver failure. Kidney Int Rep. 4:1653-57.
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5. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. 2009. A new equation to estimate glomerular filtration rate. Ann Intern Med. 150:604-612.
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7. Woodhead JL, Pellegrini L, Shoda LKM, Howell BA. 2020. Comparison of the Hepatotoxic Potential of Two Treatments for Autosomal-Dominant Polycystic Kidney Disease Using Quantitative Systems Toxicology Modeling. Pharm Res. 6;37(2):24.
8. Woodhead JL, Watkins PB, Howell BA, Siler SQ, Shoda LKM. 2017a. The role of quantitative systems pharmacology modeling in the prediction and explanation of idiosyncratic drug-induced liver injury. Drug Metabolism Pharmacokinetics. 32(1):40-45.

13 APPENDICES

13.1 Appendix 1: Chronic Kidney Disease Classification Criteria

This study uses the 2009 CKD-EPI creatinine equation (Levey et al, 2009) which is recommended by the KDIGO Clinical Practice Guidelines for Management of Chronic Kidney Disease.

The CKD-EPI equation is:

$$eGFR = 141 \times min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{Scr}{\kappa}, 1\right)^{-1.209} \times 0.993^{\text{Age}} \times 1.018\ (\text{if female}) \times 1.159\ (\text{if black}),$$

where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, age is in years, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

13.2 Appendix 2: DILI Network Causality Criteria, modified

Causality assessment scoring in the Drug-Induced Liver Injury Network (DILIN) prospective study, modified (Fontana et al, 2009)

Causality score	Likelihood (%)	Description
1 = definite	>95	Liver injury is typical for drug or herbal product ('signature' or pattern of injury, timing of onset, recovery). The evidence for causality is "beyond a reasonable doubt".
2 = highly likely	75-95	The evidence for causality is 'clear and convincing' but not definite.
3 = probable	50-74	The causality is supported by 'the preponderance of evidence' as implicating the drug but the evidence cannot be considered definite or highly likely.
4 = possible	25-49	The causality is not supported by 'the preponderance of evidence'; however, one cannot definitely exclude the possibility.
5 = unlikely	6-24	The evidence for causality is 'highly unlikely' based upon the available information.
6 = unrelated	0-5	An alternate cause was clearly established.
7 = insufficient data	Not applicable	Key elements of the drug exposure history, initial presentation, alternative diagnoses and/or diagnostic evaluation prevent one from determining a causality score.

13.3 Appendix 3: Additional Potential Hepatic Testing if Liver Chemistry Abnormalities Occur

The medical monitor may request the following additional testing if liver chemistry test abnormalities occur:

- Hematology/coagulation:
  - CBC with Diff
  - International normalized ratio (INR)

- Clinical chemistry
  - Glutamate dehydrogenase (GLDH)

- Viral hepatitis serology:
  - Hepatitis A immunoglobulin M (IgM) antibody
  - Hepatitis B surface antigen
  - Hepatitis B core antibody
  - Hepatitis C RNA
  - Hepatitis E IgM antibody (hepatitis E RNA, if available)
  - Epstein-Barr viral capsid antigen IgM antibody
  - Cytomegalovirus IgM antibody

- Autoimmune serology:
  - Total serum immunoglobulin G
  - Anti-nuclear antibody
  - Anti-smooth muscle antibody

- Ultrasound of the liver and gallbladder

13.4 Appendix 4: Liver Dysfunction Checklist

The following items will be included in a checklist to be completed by the HHC for remote visits (Part 1 only) and by the site for clinic visits (Part 1 and Part 2) when directed by the protocol. For remote visits where there are findings on Part 1 of the checklist, telehealth will be utilized to determine if a clinic visit is needed to complete Part 2.

Part 1 - Symptoms
Did the participant develop the following symptoms since the last visit?

Symptom
Fatigue
Weakness
Malaise
Loss of appetite
Nausea
Vomiting
Pain in the right upper part of the abdomen
Urine darker than usual
Itching
Yellowing of skin
Yellowing of eyes
Fever
Rash

Part 2 - Signs
Did the participant develop the following signs since the last visit?

Sign
Jaundice
Ascites
Rash
Fever
Right upper quadrant tenderness or liver enlargement
Encephalopathy

Any symptoms, signs, or an associated diagnosis deemed clinically significant based on information entered in Part 1 or Part 2 during either a remote visit or a clinic visit will be entered in the eCRF by the site as adverse events. The Investigator will determine whether a constellation of symptoms and signs in the context of all available information including

laboratory data indicate the potential presence of liver dysfunction. Otherwise, individual symptoms and signs need to be recorded as other AEs or as an alternative diagnosis. *For example,* fatigue alone may be a non-specific AE with no clear cause. *As another example,* fatigue, weakness, and vomiting occurring together may indicate a gastroenteritis. Liver dysfunction should only be considered when the totality of the evidence makes that a plausible diagnosis.

If liver dysfunction is suspected, the Investigator will communicate with the medical monitor and additional testing detailed in Section 7.2.7.1 may be recommended. Those tests are listed in Appendix 3 (Section 13.3). Additionally, the following supplemental information to complete the liver dysfunction eCRF will be collected by the site:

- Was there evidence of a concomitant viral illness?
- Did the participant's alcohol intake increase since the previous visit? If so,
    - on what date did it start?;
    - on what date did it end?;
    - what type of alcohol was ingested?; and
    - what was the total daily alcohol intake during this time?
- Did the participant start any new medications or increase any concomitant medications including herbal medications, prescribed medications, or over-the-counter medications?
- Was any AE related to liver dysfunction serious?
- Did any AE related to liver dysfunction result in discontinuation of lixivaptan treatment, either temporarily or permanently?
- What is the participant's country of birth?

Study PA-ADPKD-304:

Clinical Study Protocol Version 2.0, Dated May 20 2022

Summary of Changes

This Summary of Changes document reflects revisions incorporated into Protocol Amendment 1, Version 2.0 of the protocol. It should be used in conjunction with the tracked-changes version of the clinical study protocol amendment. Page numbers reported herein refer to the **tracked-changes** version. Revisions in Version 2.0 are shown in Track Changes. Minor editorial and document formatting revisions have not been summarized.

The main reasons for majority of the changes in this amendment are to reduce participant burden. With even longer follow up in this roll-over study, relative to the lead-in study, and stable treatment, monitoring can be less intense.

Administrative Changes

This section lists administrative changes, including changes of names or roles of companies or personnel and/or contact information. No changes listed here affect clinical decision making or consent.

Page	Section	Version 1.0, Dated 01 September 2021	Version 2.0; Dated 20 May 2022	Explanation
1	Title Page	**Medical Monitor:** David Frid, MD ICON Clinical Research Direct: (215) 616-2504 (including urgent medical issues) Fax: +1 (215) 699-6288 Email: David.Frid@iconplc.com	**Medical Monitor:** ~~David Frid~~Joyce Johnsrud, MD ICON Clinical Research ~~Direct: (215) 616-2504 (including urgent medical issues)~~ ~~Fax: +1 (215) 699-6288~~ Email: ~~David.Frid@iconplc.com~~Joyce.Johnsrud@iconplc.com	Updated contact information entered due to change in Medical monitor

Text Clarifications

This section lists corrections of typos, text changes for consistency or other clarifications. These changes do not affect clinical decision-making or consent.

Page	Section	Version 1.0, Dated 01 September 2021	Version 2.0; Dated 20 May 2022	Explanation
11	SYNOPSIS	During the 1-to-2-week Lixivaptan Re-titration Period, participants whose final dose during the Maintenance Period of the lead-in study was 100 mg BID will remain on that dose for one week and then proceed to the Maintenance Treatment Period. Participants on doses greater than 100 mg BID will be directly titrated to their final dose of the lead-in study during a second week in the re-titration period (See Table 1). Lixivaptan treatment titration and assignment will be programmed into the Interactive Response Technology (IRT) system.	During the 1-to-2-week Lixivaptan Re-titration Period, participants whose final dose during the Maintenance Period of the lead-in study was 100 mg BID or less will remain on that dose for one week and then proceed to the Maintenance Treatment Period. Participants on doses greater than 100 mg BID will be directly titrated to their final dose of the lead-in study during a second week in the re-titration period (See Table 1). Lixivaptan treatment titration and assignment will be programmed into the Interactive Response Technology (IRT) system.	Text revised to reflect that final Lixivaptan dose may be 100 mg BID or less.
18	SYNOPSIS Table 3 Schedule of Procedures	**Assessments** Vital signs[e] Body weight[f] Physical examination[g] Pregnancy test (WOCBP only)[h] Chemistry Blood Sample[i]	**Assessments** Vital signs[eg] Body weight[fh] Physical examination[gi] Pregnancy test (WOCBP only)[hj] Chemistry Blood Sample[ik]	Footnote numbering has been updated to reflect the additional footnotes added in this amendment in Table 3.
18	SYNOPSIS Table 3 Schedule of Procedures	Screening Period[a] PA-ADPKD-303 Study Visits	Screening Period[a] PA-ADPKD-303 Study ~~Visits~~	Deleted 'Visits' from 'PA-ADPKD-303 Study Visits' header to avoid potential misunderstanding that V1 Study visit listed in that column is from 'PA-ADPKD-303 Study. The V1 refers to the 'PA-ADPKD-304 Study

Page	Section	Version 1.0, Dated 01 September 2021	Version 2.0; Dated 20 May 2022	Explanation
				Visit.
20	SYNOPSIS Footnotes of Table 3 Schedule of Procedures	[d] Visits designated as "Laboratory Only" may be completed at the clinic or remotely by a home healthcare clinician or by a designated third-party that will draw and process samples for shipment to the central laboratory where available and approved. Otherwise, the visits will be completed at the study clinic.	[d] Visits designated as "Laboratory Only" may be completed at the clinic or remotely by a home healthcare clinician or by a designated third-party that will draw and process samples for shipment to the central laboratory where available and approved. ~~Otherwise, the visits will be completed at the study clinic.~~	Footnote text revised to remove redundant language.
34	4.2.5 Methods to Prevent Loss to Follow-up	The Investigator must make every attempt to follow-up participants who have withdrawn from the study at any time and for any reason. When a participant is "lost to follow-up" (i.e., fails to return for study visits or complete one or more scheduled remote site visits), a reasonable effort (3 documented phone calls or 2 phone calls and 2 text messages [if the participant has a mobile phone], on separate occasions, and a follow-up letter sent by registered mail) should be made to contact him/her to determine a reason for the failure to return or complete remote visit(s). If the participant cannot be reached, he/she should be identified as "lost to follow-up" in the eCRF.	The Investigator must make every attempt to follow-up participants who have withdrawn from the study at any time and for any reason. When a participant is "lost to follow-up" (i.e., fails to return for study visits or complete one or more scheduled remote ~~site~~ visits), a reasonable effort (3 documented phone calls or 2 phone calls and 2 text messages [if the participant has a mobile phone], on separate occasions, and a follow-up letter sent by registered mail) should be made to contact him/her to determine a reason for the failure to return or complete remote visit(s). If the participant cannot be reached, he/she should be identified as "lost to follow-up" in the eCRF.	Revised remote site visits to remote visits for consistency.
77	13.4 Appendix 4: Liver Dysfunction Checklist	The following items will be included in a checklist to be completed by the HHC for remote visits (Part 1 only) and by the site for clinic visits (Part 1 and Part 2) when directed by the protocol. For remote visits where there are findings on Part 1 of the checklist, telemedicine will be utilized to determine if a clinic visit is needed to complete Part 2.	The following items will be included in a checklist to be completed by the HHC for remote visits (Part 1 only) and by the site for clinic visits (Part 1 and Part 2) when directed by the protocol. For remote visits where there are findings on Part 1 of the checklist, telehealth~~medicine~~ will be utilized to determine if a clinic visit is needed to complete Part 2.	"Telemedicine" replaced with "telehealth" usage for consistency.
Multiple	Global	In-clinic visit	~~In-~~Clinic visit	"In-Clinic visit" replaced with

Page	Section	Version 1.0, Dated 01 September 2021	Version 2.0; Dated 20 May 2022	Explanation
				'Clinic visit' throughout the protocol for consistency.
Multiple	Global	home healthcare clinician	~~home healthcare clinician~~ HHC	'home healthcare clinician' abbreviated to HHC throughout the protocol for consistency.

Clinically-relevant Changes

This section describes changes that affect safety or study conduct.

Page	Section	Version 1.0, Dated 01 September 2021	Version 2.0; Dated 20 May 2022	Rationale
13	SYNOPSIS Study Period Description and Estimated Duration:	Maintenance Treatment Period: Following completion of the Lixivaptan Re-titration Period, participants will continue into the open-label Maintenance Treatment Period following completion of Visit 3 assessments for up to 104 weeks. Participants will be assessed at study visits scheduled every 12 weeks but will have required liver chemistry testing every 4 weeks; those visits occurring between the 12-week study visits are designated as "laboratory-only visits". Where available and approved, the laboratory-only visits may be conducted remotely by a home healthcare clinician or by a designated third-party that will process samples for shipment to the central laboratory. In addition, liver chemistry tests may be drawn in the	Maintenance Treatment Period: Following completion of the Lixivaptan Re-titration Period, participants will continue into the open-label Maintenance Treatment Period following completion of Visit 3 assessments for up to 104 weeks. Participants will be assessed at study visits scheduled every 12 weeks but will have required liver chemistry testing every 4 weeks; those visits occurring between the 12-week study visits are designated as "laboratory-only visits". Where available and approved, the laboratory-only visits may be conducted remotely by a H~~h~~ome H~~h~~ealthcare C~~c~~linician (HHC) or by a designated third-party that will process samples for shipment to the central laboratory. In addition, liver chemistry tests may be drawn in the clinic if that is more convenient for the participant. The	Categorized V6, V12, V18, and V24 (Weeks 12, 36, 60, and 84, respectively) visits as Clinic or Remote Visits (can be performed either on-site or remotely by a Home Health Clinician (HHC)) to reduce participant burden.

Page	Section	Version 1.0, Dated 01 September 2021	Version 2.0; Dated 20 May 2022	Rationale
		clinic if that is more convenient for the participant.	12 -week study visits at Weeks 12, 36, 60, and 84 can be performed either on-site or remotely by an HHC, if available and approved.	
18	SYNOPSIS Table 3 Schedule of Procedures	Follow-up Period (Up to 4 weeks ± 3 days) Day 8 + 3 days after last dose (V30) Day 12 to 24 days after last dose (V31) Day 28 ± 3 days after last dose (V32)	Follow-up Period (Up to 4 weeks ± 3 days) "Laboratory Only Visits[d]"- Day 8 + 3 days after last dose (V30) Day 12 to 24 days after last dose (V31) "Study Visits"- Day 28 ± 3 days after last dose (V32)	Categorized 2 follow-up visits (V30 and V31) to Laboratory Only Visits to reduce participant burden.
		Lixivaptan Re-titration Period[b] (1 to 2 weeks ± 3 days) (Week -1 to Week 0) V2	Lixivaptan Re-titration Period[b] Telehealth Visit[e] (1 to 2 weeks ± 3 days) (Week -1 to Week 0) V2[e]	Categorized V2 visit as a Telehealth Visit (with site staff) to reduce participant burden.
		Lixivaptan Re-titration Period[b] (1 to 2 weeks ± 3 days) (Week -1 to Week 0) V3/Last	Lixivaptan Re-titration Period[b] Clinic or Remote Visit[f] (1 to 2 weeks ± 3 days) (Week -1 to Week 0) V3/Last[f]	Categorized V3/ Last visit as Clinic or Remote Visit (can be performed either on-site or remotely by a Home Health Clinician (HHC)) to reduce participant burden.
		Weeks 12, 24, 36, 48, 60, 72, 84, 96	Weeks 12[f], 24, 36[f], 48, 60[f], 72, 84[f], 96[f]	Categorized Weeks 12, 36, 60, 84 and 96 as Clinic or Remote Visits (can be performed either on-site or remotely by a Home Health Clinician (HHC)) to reduce participant burden.
		V6, V9, V12, V15, V18, V21, V24, V27	V6[f], V9, V12[f], V15, V18[f], V21, V24[f], V27[f]	Categorized V6, V12, V18, V24 and V27 visits as Clinic or Remote Visits (can be performed either on-site or remotely by a Home Health

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				Clinician (HHC)) to reduce participant burden.
		Lixivaptan Re-titration Period[b] (1 to 2 weeks ± 3 days) (Week -1 to Week 0) V2 X (Vital Signs[e])	Lixivaptan Re-titration Period[b] (1 to 2 weeks ± 3 days) (Week -1 to Week 0) V2[e] ~~X~~ (Vital Signs[~~eg~~])	The safety assessment (Vital Signs) during Visit 2 was removed to reduce participant burden.
		Study Visits (every 12 weeks ± 5 days) V9, V15, V21, V27 (Physical Examination[f] and ECG)	Study Visits (every 12 weeks ± 5 days) V9, V15, V21, ~~V27~~ (Physical Examination[~~f~~h] and ECG)	During the visit 27, physical examination and ECG safety assessments were removed. Assessments made at V21 and V32 (32 weeks apart) are considered sufficient to assess these parameters.
19		Lixivaptan Re-titration Period[b] (1 to 2 weeks ± 3 days) (Week -1 to Week 0) V2 X (Lixivaptan dispensation)	Lixivaptan Re-titration Period[b] (1 to 2 weeks ± 3 days) (Week -1 to Week 0) V2[e] ~~X~~ (Lixivaptan dispensation)	The activity (Lixivaptan dispensation) during Visit 2 was removed as Visit 2 will now be via telehealth visit, the drug dispensed at Visit 1 will be sufficient to cover the full Lixivaptan Re-titration Period.
20	SYNOPSIS Footnotes of Table 3 Schedule of Procedures	[e] Vital signs after the participant has been sitting for 5 minutes include sitting heart rate and sitting blood pressure. [f] Weight will be measured at Visit 24 (PA-ADPKD-303), Visit 3, Visit 15, Visit 29/ET, and Visit 32. Weight may be measured at any other visit to assess	[e] Visit 2 is a telehealth visit (e.g., telemedicine virtual visit, telephone or video call (without recording)) with site staff. Visit 2 is only applicable to participants whose final dose in the lead-in study was greater than 100 mg BID. At telehealth Visit 2, lixivaptan treatment compliance will be monitored and lixivaptan reconciliation will occur at Visit 3.	Footnote text has been updated to make consistent with revisions in Visit Designations in Table. • Categorized visit 2 as a Telehealth Visit (with site staff) to reduce participant burden. • Categorized V3, V6, V12, V18, V24, and V27 visits as Clinic or

		hydration status as necessary. [g] A brief physical examination will be performed at Visit 1 (Visit 27 of lead-in study), Visit 9, Visit 15, Visit 21, Visit 27, and Visit 32. A full physical examination will be completed at Visit 29/ET. Additional physical examinations will be performed only for assessment of signs or symptoms reported by the participant that might require further evaluation. [h] Routine pregnancy testing for WOCBP will be performed locally on urine. All positive urine results will be confirmed by a serum pregnancy test at the central lab. [i] Chemistry blood samples will be collected according to the schedule in Table 3: • A complete chemistry panel includes the following parameters: albumin; blood urea nitrogen (urea); calcium; chloride; carbon dioxide (CO2); creatinine, enzymatic; glucose; phosphorous; potassium; protein; sodium; uric acid. • The liver chemistry panel includes alkaline phosphatase; ALT; AST; bilirubin (total and direct). • All serum creatinine determinations will be performed by the central laboratory.	[f] Study Visits are more extensive than laboratory only or telehealth visits. Study Visits designated as "Clinic or Remote Visits" can be performed either on-site or remotely by a Home Health Clinician (HHC). Visits 3, 6, 12, 18, 24 and 27 are designated as "Clinic or Remote Visits". All other Study Visits are Clinic Visits. ~~[e]~~[g] Vital signs after the participant has been sitting for 5 minutes include sitting heart rate and sitting blood pressure. ~~[f]~~[h] Weight will be measured at Visit 24 (PA-ADPKD-303), Visit 3, Visit 15, Visit 29/ET, and Visit 32. Weight may be measured at any other visit to assess hydration status as necessary. ~~[g]~~[i] A brief physical examination will be performed at Visit 1 (Visit 27 of lead-in study), Visit 9, Visit 15, Visit 21, ~~Visit 27,~~ and Visit 32. A full physical examination will be completed at Visit 29/ET. Additional physical examinations will be performed only for assessment of signs or symptoms reported by the participant that might require further evaluation. ~~[h]~~[j] Routine pregnancy testing for WOCBP will be performed locally on urine. All positive urine results will be confirmed by a serum pregnancy test at the central lab. [~~i~~]k Chemistry blood samples will be collected according to the schedule in Table 3: • A complete chemistry panel includes the following parameters:	Remote Visits (can be performed either on-site or remotely by a Home Health Clinician (HHC)) to reduce participant burden. • During the visit 27, physical examination and ECG safety assessments were removed. Assessments made at V21 and V32 (32 weeks apart) are considered sufficient to assess these parameters. • Numbering of subsequent footnotes has been updated.

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			albumin; blood urea nitrogen (urea); calcium; chloride; carbon dioxide (CO2); creatinine, enzymatic; glucose; phosphorous; potassium; protein; sodium; uric acid. • The liver chemistry panel includes alkaline phosphatase; ALT; AST; bilirubin (total and direct). • All serum creatinine determinations will be performed by the central laboratory.	
30	3.1.2 Detailed Study Design	Maintenance Treatment Period: Following completion of the Lixivaptan Re-titration Period, participants will continue into the open-label Maintenance Treatment Period following completion of Visit 3 assessments for up to 104 weeks. Participants will be assessed at study visits scheduled every 12 weeks with assessments but will have required liver chemistry testing every 4 weeks at visits designated as "laboratory-only visits". Where available and approved, the laboratory-only visits may be conducted remotely by a home healthcare clinician or by a designated third-party that will process samples for shipment to the central laboratory. In addition, the liver chemistry tests may be drawn in the clinic if that is more convenient. Follow-up Period: Three visits will occur over 4 weeks	Maintenance Treatment Period: Following completion of the Lixivaptan Re-titration Period, participants will continue into the open-label Maintenance Treatment Period following completion of Visit 3 assessments for up to 104 weeks. Participants will be assessed at study visits scheduled every 12 weeks with assessments but will have required liver chemistry testing every 4 weeks at visits designated as "laboratory-only visits". Where available and approved, the laboratory-only visits may be conducted remotely by an HHC ~~home healthcare clinician~~ or by a designated third-party that will process samples for shipment to the central laboratory. In addition, the liver chemistry tests may be drawn in the clinic if that is more convenient. Furthermore, certain study	Text modified as some visits are now categorized as "Clinic or Remote Visits" or as "laboratory only" visits to reduce participant burden.

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		following the last dose of lixivaptan treatment in order to obtain final assessments. Starting with the 8th day after the last dose of lixivaptan treatment, serum creatinine will be assessed at 3 time points (no less than 24 hours apart between each sampling) over a period of up to 28 days post last dose of lixivaptan. NOTE: If a participant terminates the study early (ET), an eGFR determination from serum creatinine obtained at 3 time points over a period of up to 28 days post last dose, will be carried out.	visits can be performed by an HHC. Follow-up Period: Three visits will occur over 4 weeks following the last dose of lixivaptan treatment in order to obtain final assessments. Starting with the 8th day after the last dose of lixivaptan treatment, serum creatinine will be assessed at 3 time points (no less than 24 hours apart between each sampling) over a period of up to 28 days post last dose of lixivaptan. Certain follow-up visits are designated as laboratory-only visits. NOTE: If a participant terminates the study early (ET), an eGFR determination from serum creatinine obtained at 3 time points over a period of up to 28 days post last dose, will be carried out.	
36	5.1.3 Lixivaptan Packaging, Labeling, and Storage	Lixivaptan should be stored at the study site in its original packaging in a secure, locked area under the responsibility of the Investigator or other authorized individual. At the study site, lixivaptan should be stored in accordance with the specifications detailed in the study pharmacy manual. Once lixivaptan is dispensed, the participant should be instructed to store it in its original packaging and in accordance with lixivaptan treatment labelling at all times until ready to take.	Lixivaptan should be stored at the study site in its original packaging in a secure, locked area under the responsibility of the Investigator or other authorized individual. At the study site, lixivaptan should be stored in accordance with the specifications detailed in the study pharmacy manual. Once lixivaptan is dispensed, the participant should be instructed to store it in its original packaging and in accordance with lixivaptan treatment labelling at all times until ready to take. For study visits conducted remotely (not applicable to laboratory only visits), study drug will be dispensed and shipped from the study site to the participant's home, or to an	Text has been added to reflect Lixivaptan dispensing procedure during remote visits; remote visits were added to reduce patient burden.

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			alternate location pre-specified by the participant, via an experienced courier approved by the Sponsor. Participants will be provided with written instructions to securely store the study drug in its original packaging under the conditions described above and not to open the package until the HHC arrives.	
38	5.6 Treatment Compliance	Dispensing of lixivaptan treatment will be done initially at Visit 1. Subsequently, dispensing of lixivaptan treatment and reconciliation will occur at Visit 2 (if applicable) and Visit 3 during the Re-titration Period and every 12 weeks, at in-clinic visits, during the Maintenance Treatment Period.	Dispensing of lixivaptan treatment will be done initially at Visit 1. Subsequently, dispensing of lixivaptan treatment and reconciliation will occur at ~~Visit 2 (if applicable) and~~ Visit 3 during the Re-titration Period and every 12 weeks, at ~~in-~~ clinic or direct-to-participants in advance of remote visits, during the Maintenance Treatment Period.	Text has been revised to reflect Lixivaptan dispensing procedure during remote visits to reduce participant burden
42	6 TIMING OF STUDY PROCEDURES	The timing of study procedures is presented in Table 3. Scheduled quarterly visits must occur in the Investigator's clinic while other "Laboratory Only" visits at 4-week intervals can be completed remotely by an HHC or by an approved designated third-party.	The timing of study procedures is presented in Table 3. Scheduled quarterly visits (except for Visits 9, 15 and 21) ~~must~~ may occur in the Investigator's clinic or remotely with an HHC. Visits 9, 15 and 21 must occur in the Investigator's clinic. ~~while o~~Other "Laboratory Only" visits at 4-week intervals can be completed remotely by an HHC or by an approved designated third-party.	Text has been added to reflect remote visits, which have been added to reduce participant burden.
42 and 43	6.1.1. Visit 1/Visit 27 of PA-ADPKD-303	○ If all study entry criteria are met, contact the IRT to record the participant's completion of Visit 1 and obtain a lixivaptan kit number assignment to initiate the Re-titration Period and proceed as follows: ▪ Dispense lixivaptan and have participant take the first dose	○ If all study entry criteria are met, contact the IRT to record the participant's completion of Visit 1 and obtain ~~a~~ lixivaptan kit number assignments to initiate the Re-titration Period. Participants whose final dose during PA-ADPKD-303 was ≤100mg BID should receive sufficient lixivaptan for a	Text has been added to reflect Lixivaptan dispensing procedure during remote visits, which have been added to reduce participant burden.

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		when he/she returns home from the clinic. Instruct the participant to take 2 capsules (100 mg) BID approximately 10 hours apart, e.g., 8 AM and 6 PM. (Instruct participants whose final dose was 50 mg BID during the lead-in study, to take 1 capsule [50 mg] BID) ▪ Remind the participant to expect aquaretic effects and to maintain fluid intake to prevent dehydration	7 + 3-day interval in accordance with Table 2. Participants whose final dose during PA-ADPKD-303 was >100mg BID, should receive sufficient lixivaptan for a 14 + 3-day interval, including a dose escalation that will begin following completion of Visit 2, in accordance with Table 2. P~~and p~~roceed as follows: ▪ Dispense lixivaptan and have participant take the first dose when he/she returns home from the clinic. Instruct the participant to take 2 capsules (100 mg) BID approximately 10 hours apart, e.g., 8 AM and 6 PM. (Instruct participants whose final dose was 50 mg BID during the lead-in study, to take 1 capsule [50 mg] BID) ▪ Remind the participant to expect aquaretic effects and to maintain fluid intake to prevent dehydration	
43	6.2 Re-titration Period	○ The Re-titration Period will last from 1 to 2 weeks. Participants will self-administer lixivaptan at home. Participants whose final dose during the Maintenance Period of the lead-in study was ≤100 mg BID will remain on that dose for 1 week and then proceed to Visit 3. Participants on doses greater than 100 mg BID will be directly titrated to their final dose of the lead-in study at Visit 2 in the Re-titration period, in accordance with Table 1.	○ The Re-titration Period will last from 1 to 2 weeks. Participants will self-administer lixivaptan at home. Participants whose final dose during the Maintenance Period of the lead-in study was ≤100 mg BID will remain on that dose for 1 week and then proceed to Visit 3. Participants on doses greater than 100 mg BID will be directly titrated to their final dose of the lead-in study following completion of the telehealth visit at Visit 2 in the Re-titration period and remain on that dose for 1 week, in accordance with Table 1.	Text has been added to reflect Lixivaptan dispensing procedure during remote visits, which have been added to reduce participant burden.

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43	6.2.1.1 Visit 2	Participants whose final dose at the end of the lead-in study was >100 mg BID will report to the clinic for Visit 2 of the Re-titration Period. Participants should bring any remaining lixivaptan treatment into the clinic. The following procedures will be performed: ○ Check AEs and SAEs ○ Assess clinically for liver dysfunction (symptoms and signs) in accordance with the checklist and instructions in Appendix 4 (Section 13.4) ○ Collect and review concomitant medication information ○ Review lixivaptan treatment compliance/reconciliation ○ Check vital signs (sitting blood pressure and heart rate) ○ Contact the IRT to record the visit and obtain a lixivaptan kit number assignment for week 2 of the Re-titration Period ○ Dispense lixivaptan and instruct participant on appropriate dose based on the dose level guide in Table 2 ○ Schedule the participant for Visit 3 to occur in 1 week and remind the participant to take adequate fluids. Provide the participant with an appointment reminder card and any written instructions.	Participants whose final dose at the end of the lead-in study was >100 mg BID will have a telehealth visit ~~report to the clinic for~~ at Visit 2 of the Re-titration Period. ~~Participants should bring any remaining lixivaptan treatment into the clinic.~~ The following procedures will be performed: ○ Check AEs and SAEs ○ Assess ~~clinically for~~ liver dysfunction (symptoms ~~and signs~~) in accordance with Part 1 of the checklist and instructions in Appendix 4 (Section 13.4) ○ Collect and review concomitant medication information ○ Review lixivaptan treatment compliance (capsules to be reconciled during Visit 3)~~/reconciliation~~ ~~○ Check vital signs (sitting blood pressure and heart rate)~~ ○ Contact the IRT to record the visit~~ and obtain a lixivaptan kit number assignment for week 2 of the Re-titration Period~~ ○ ~~Dispense lixivaptan and i~~Instruct the participant to increase his/her dose of lixivaptan ~~on appropriate dose~~ based on the dose level guide in Table 2 ○ Schedule the participant for Visit 3 to occur in 1 week and remind the participant to take adequate fluids. Provide the participant with an	Text has been revised to reflect Lixivaptan dispensing procedure during remote visits, which have been added to reduce participant burden.

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			appointment reminder card and any written instructions.	
44	6.2.1.2 Visit 3/Last Titration Visit	Participants will report to the clinic for assessments for the last visit of the Re-titration Period. Dosing will continue for the remainder of the study at the level the participant was receiving at the end of the Maintenance Period of the lead-in study. If there is difficulty with tolerability, the dose may be temporarily reduced, participant may then enter the Maintenance Treatment Period and the dose will be readdressed at the next clinic visit (Visit 6). Dosing reductions for participants on Level 2 (100 mg BID or less) will require prior approval from the medical monitor. Participants should bring any remaining lixivaptan treatment into the clinic.	Participants will either report to the clinic or have a remote visit by an HHC for assessments for the last visit of the Re-titration Period. Dosing will continue for the remainder of the study at the level the participant was receiving at the end of the Maintenance Period of the lead-in study. If there is difficulty with tolerability, the dose may be temporarily reduced, participant may then enter the Maintenance Treatment Period and the dose will be readdressed at the next clinic visit (Visit 6). Dosing reductions for participants on Level 2 (100 mg BID or less) will require prior approval from the medical monitor. Participants should bring any remaining lixivaptan treatment into the clinic if having a site visit. If the visit is a remote visit, participant should give any remaining lixivaptan to the HHC.	Revised this section to indicate that V3 is a remote visit, which have been added to reduce participant burden.
45	6.3 Maintenance Treatment Period	The Maintenance Treatment Period will last 104 weeks (Visit 4 to Visit 29). Visits designated as "laboratory only" may be completed at the clinic or conducted remotely by an HHC or by a designated third-party who will draw and process samples for shipment to the central laboratory where available and approved. Laboratory only visits include Visits 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25,	The Maintenance Treatment Period will last 104 weeks (Visit 4 to Visit 29). Visits designated as "laboratory only" may be completed at the clinic or conducted remotely by an HHC or by a designated third-party who will draw and process samples for shipment to the central laboratory where available and approved. Laboratory only visits include Visits 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, and 28. ~~The remaining V~~visits 9, 15, 21	Revised to indicate that V6, V12, V18, V24 and V27 are now designated as Remote visits, which have been added to reduce participant burden.

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		26, and 28. The remaining visits will be completed at the study clinic.	and 29 will be completed at the study clinic~~.~~, while the remaining visits designated as "clinic or remote visits" (Visits 6, 12, 18, 24 and 27) may be performed either on-site or remotely by an HHC.	
45	6.3.1 Visits 4 to 28	In-clinic study visits will occur every 12 weeks ± 5 days. Laboratory only visits will occur every 4 weeks ± 5 days on weeks when there is not an in-clinic visit.	~~In-clinic s~~Study visits will occur every 12 weeks ± 5 days. Laboratory only visits will occur every 4 weeks ± 5 days on weeks when there is not a~~n in-~~clinic or remote visit.	Clarification text added to indicate visits that are now designated as Clinic or Remote visits, which have been added to reduce participant burden.
45	6.3.1 Visits 4 to 28	6.3.1.2 Visits 6, 9, 12, 15, 18, 21, 24, and 27/In-clinic visits	6.3.1.~~2~~3 Visits ~~6, 9, 12,~~ 15~~, 18,~~and ~~-21, 24, and 27~~/ ~~In-C~~clinic V~~v~~isits	The visits 6, 12, 18, 24 and 27 are now categorized as Remote Visits (can be performed either on-site or remotely by a Home Health Clinician (HHC)) to reduce participant burden. Converted the clinic visits as Section 6.3.1.3 and added the Remote visits as Section 6.3.1.2.
45	6.3.1.2 Visits 6, 9, 12, 18, 21, and 24/Remote visits		6.3.1.2 Visits 6, 12, 18, 24, and 27/Clinic or Remote Visits Visits 6, 12, 18, 24 and 27 can be performed either on-site or remotely by an HHC. The following procedures will be performed at each clinic or remote visit: • Check AEs and SAEs • Assess liver dysfunction (signs and symptoms at clinic visits (Part 1 and Part 2 of the checklist); symptoms only at remote visits (Part 1 of the checklist)) in	Added Remote Visits as Section 6.3.1.2 to distinguish the clinic and remote visits and list of procedures added. Removed safety assessments during V9 and V21 to reduce patient burden; safety assessments obtained at a maximum time period of every 24-32 months are considered sufficient to monitor those safety parameters

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			accordance with instructions in Appendix 4 (Section 13.4)
			• Collect and review concomitant medication information
			• Review lixivaptan treatment compliance/reconciliation
			• Check vital signs (sitting blood pressure and heart rate)
			• Collect urine to conduct a pregnancy test in WOCBP
			• Collect blood samples for
			  ○ Complete chemistry panel
			  ○ Liver chemistry panel
			• Contact the IRT at each visit to obtain lixivaptan kit number assignments and complete the visit
			• Dispense 12-week supply of lixivaptan and instruct participant to take the appropriate dose BID approximately 10 hours apart, e.g., 8 AM and 6 PM
			• Schedule the participant to return in 4 weeks for his/her next laboratory visit (if not already scheduled); confirm where the visit will take place. Also, schedule participant for the next clinic or remote visit in 12 weeks. At each visit, remind the participant to take adequate fluids. Provide the participant with an appointment reminder card(s) and any written instructions. Note: Visit 29 should	

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			be scheduled approximately 8 weeks from Visit 27. Dosing instructions should be tailored accordingly.	
46	6.3.1.2 Visits 6, 9, 12, 15, 18, 21, 24, and 27/In-clinic visits	Section 6.3.1.2 Visits 6, 9, 12, 15, 18, 21, 24, and 27/In-clinic visits Participants should bring any remaining lixivaptan treatment into the clinic. The following procedures will be performed at each in-clinic visit: • Check AEs and SAEs • Assess clinically for liver dysfunction (symptoms) in accordance with the checklist and instructions in Appendix 4 (Section 13.4) • Collect and review concomitant medication information • Review lixivaptan treatment compliance/reconciliation • Check vital signs (sitting blood pressure and heart rate) • Collect body weight (Visit 15 only) • Perform a brief physical examination (Visits 9, 15, 21, and 27 only) • Perform a 12-lead ECG (Visits 9, 15, 21, and 27 only) • Collect urine to conduct a pregnancy test in WOCBP	Section 6.3.1.32 Visits ~~6,~~ 9, ~~12,~~ 15~~,~~ ~~18,~~and 21, ~~24, and 27~~/~~In-C~~clinic V~~v~~isits Participants should bring any remaining lixivaptan treatment into the clinic. The following procedures will be performed at each ~~in-~~clinic visit: • Check AEs and SAEs • Assess clinically for liver dysfunction (symptoms) in accordance with the checklist and instructions in Appendix 4 (Section 13.4) • Collect and review concomitant medication information • Review lixivaptan treatment compliance/reconciliation • Check vital signs (sitting blood pressure and heart rate) • Collect body weight (Visit 15 only) • Perform a brief physical examination ~~(Visits 9, 15, 21, and 27 only)~~ • Perform a 12-lead ECG ~~(Visits 9, 15, 21, and 27 only)~~ • Collect urine to conduct a pregnancy test in WOCBP	Revised Section 6.3.1.2 as 6.3.1.3 to distinguish clinic visits (V9, V15 and V21) from remote visits (V6, V12, V18, V24 and V27 visits) and revised list of procedures. Remote visits have been introduced to reduce patient burden.

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		• Collect urine for urinalysis (Visit 15 only)
		• Collect blood samples for
		  ○ Complete chemistry panel
		  ○ Liver chemistry panel
		  ○ Hematology (Visits 9, 15 and 21 only)
		• Dispense 12-week supply of lixivaptan and instruct participant to take the appropriate dose BID approximately 10 hours apart, e.g., 8 AM and 6 PM
		• Schedule the participant to return in 4 weeks for his/her next laboratory visit (if not already scheduled); confirm where the visit will take place. Also, schedule participant for the next in-clinic visit in 12 weeks. At each visit, remind the participant to take adequate fluids. Provide the participant with an appointment reminder card(s) and any written instructions.
			• Collect urine for urinalysis (Visit 15 only)
			• Collect blood samples for
			  ○ Complete chemistry panel
			  ○ Liver chemistry panel
			  ○ Hematology ~~(Visits 9, 15 and 21 only)~~
			• Contact the IRT at each visit to obtain lixivaptan kit number assignments and complete the visit
			• Dispense 12-week supply of lixivaptan and instruct participant to take the appropriate dose BID approximately 10 hours apart, e.g., 8 AM and 6 PM
			• Schedule the participant to return in 4 weeks for his/her next laboratory visit (if not already scheduled); confirm where the visit will take place. Also, schedule participant for the next ~~in-~~clinic or remote visit in 12 weeks. At each visit, remind the participant to take adequate fluids. Provide the participant with an appointment reminder card(s) and any written instructions.	

47	6.4 Follow-up Period	The Follow-up Period will last 28 days and include 3 visits (Visit 30, Visit 31, and Visit 32).	The Follow-up Period will last 28 days and include 3 visits (Visit 30, Visit 31, and Visit 32). Visits 30 and 31 are designated as "laboratory only visits" and may be completed at the clinic or conducted remotely by an HHC or by a designated third-party who will draw and process	Updated this section to indicate that Visit 30 and 31 are Laboratory Only Visit; these Laboratory Only visits will reduce patient burden.

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			samples for shipment to the central laboratory where available and approved.	
47	6.4.1 Visit 30	The following procedures will be performed at Visit 30: • Check AEs and SAEs • Assess clinically for liver dysfunction (symptoms and signs) in accordance with the checklist and instructions in Appendix 4 (Section 13.4) • Collect and review concomitant medication information • Collect a blood sample for serum creatinine Schedule the participant to return to the clinic for Visit 31, in 12 to 24 (± 3) days after the last dose of lixivaptan treatment.	The following procedures will be performed at Visit 30 ("laboratory only" visit): • ~~Check AEs and SAEs~~ • ~~Assess clinically for liver dysfunction (symptoms and signs) in accordance with the checklist and instructions in Appendix 4 (Section 13.4)~~ • ~~Collect and review concomitant medication information~~ • Collect a blood sample for serum creatinine • Site personnel to contact the IRT to register visit • Schedule the participant for the next visit ~~to return to the clinic for~~ (Visit 31) to occur ~~,~~ ~~in~~ 12 to 24 (± 3) days after the last dose of lixivaptan treatment.	Updated this section to indicate that Visit 30 is Laboratory Only Visit. This Laboratory Only visit will reduce patient burden. Revised the list of procedures and added IRT information to align with "laboratory only procedures"
48	6.4.2 Visit 31	The following procedures will be performed at Visit 31: • Check AEs and SAEs • Assess clinically for liver dysfunction (symptoms and signs) in accordance with the checklist and instructions in Appendix 4 (Section 13.4) • Collect and review concomitant medication information	The following procedures will be performed at Visit 31 ("laboratory only" visit): • ~~Check AEs and SAEs~~ • ~~Assess clinically for liver dysfunction (symptoms and signs) in accordance with the checklist and instructions in Appendix 4 (Section 13.4)~~ • ~~Collect and review concomitant medication information~~	Updated this section to indicate that Visit 31 is Laboratory Only Visit. This Laboratory Only visit will reduce patient burden. Revised the list of procedures and added IRT information to align with "laboratory only procedures"

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		• Collect a blood sample for serum creatinine Schedule the participant to return to the clinic for Visit 32, in 28 (± 3) days after the last dose of lixivaptan treatment.	• Collect a blood sample for serum creatinine • Site personnel to contact the IRT to register visit • Schedule the participant to return to the clinic for Visit 32 to occur~~, in~~ 28 (± 3) days after the last dose of lixivaptan treatment.	