SYNOPTIC CLINICAL STUDY REPORT

A Phase 3 Study of the Efficacy and Safety of Lixivaptan in Participants with Autosomal Dominant Polycystic Kidney Disease Consisting of a 1-year Double-blind, Placebo-controlled, Randomized Phase and a 1-year Open-label Phase: The ACTION Study

1 TITLE PAGE

Protocol Number:	PA-ADPKD-301
Study Phase:	Phase 3
First Participant Enrolled:	30 November 2021
Last Participant Completed:	03 August 2022
Principal Investigator:	Vicente E. Torres, MD, PhD Director of Mayo Clinic Translational Polycystic Kidney Disease Center Division of Nephrology and Hypertension, Mayo Clinic Rochester, MN 55905 USA
Sponsor Responsible Medical Person:	Neil Shusterman, MD Chief Medical Officer
Sponsor:	Palladio Biosciences Inc.
Document Date:	15 November 2022
This study was conducted in accordance with the International Council on Harmonization (ICH), Good Clinical Practices (GCPs) and the Declaration of Helsinki, and complies with the obligations and requirements of the Clinical Investigator and other requirements as listed in Title 21 of the United States Code of Federal Regulations (CFR) and other applicable regulations	

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Name of Sponsor/Company: Palladio Biosciences Inc	**Individual Study Table** Referring to Part of the Dossier: **Volume**: <Enter number> **Page**: <Enter number>	(For National Authority Use only)
Name of Finished Product Lixivaptan		
Name of Active Ingredient N-[3-chloro-4-(6,11-dihydropyrrolo[2,1-c][1,4]benzodiazepine-5-carbonyl)phenyl]-5-fluoro-2-methylbenzamide		

Title of Study: A Phase 3 Study of the Efficacy and Safety of Lixivaptan in Participants with Autosomal Dominant Polycystic Kidney Disease Consisting of a 1-year Double-blind, Placebo-controlled, Randomized Phase and a 1-year Open-label Phase: The ACTION Study

Principal/Lead Investigator:

Vicente E. Torres, MD, PhD

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Study centers:

Planned: Approximately 250 sites worldwide.

Active (screened at least one participant) at time of early termination of study: 24 sites: United States (15 sites), Australia (1 site), Bulgaria (2 sites), Hungary (2 sites), Poland (1 site), Spain (1 site), and Turkey (2 sites).

Publication (reference): Shusterman NH, Richardson ER, Castellana JV, Pellegrini L. A phase 3 clinical program with the novel vasopressin V2 receptor antagonist lixivaptan in patients with autosomal dominant polycystic kidney disease (ADPKD). Poster presented at ASN 2019 Kidney Week meeting, November 08, 2019;Washington, DC, https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3253072

Date of First Participant Enrollment:30 November 2021 **Date of Early Study Termination:** 02 June 2022 **Date of Last Participant Completed**: 03 August 2022	**Phase of Development**: Phase 3

OBJECTIVES: The primary objectives of this study were:

Part 1 (Year 1):

The primary efficacy objective of Part 1 was:

- To demonstrate the efficacy of lixivaptan compared to placebo in the slowing of deterioration in kidney function in participants with ADPKD as demonstrated by the annualized change from baseline in estimated glomerular filtration rate (eGFR).

The key safety objective of Part 1 was:

- To compare the incidences of liver chemistry test elevations in participants randomized to lixivaptan with participants randomized to placebo.

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The secondary efficacy objectives of Part 1 were:

- To compare the rate of change (slope) in on-treatment eGFR in participants treated with lixivaptan to participants treated with placebo;
- To assess the effect of lixivaptan on total kidney volume (TKV) as measured by magnetic resonance imaging (MRI) compared to placebo.

The secondary safety objective of Part 1 was:

- To assess the non-hepatic safety and tolerability of lixivaptan.

The health outcomes-related objectives of Part 1 were:

- To evaluate medical resource utilization (e.g., medication use/changes; unplanned office visit; urgent care and emergency department usage; and hospitalizations) resulting from clinical events in participants randomized to lixivaptan compared with those on placebo and assess which events are driving any observed differences in medical resource utilization between lixivaptan and placebo.
- To evaluate the change from baseline in domain scores of the ADPKD Impact Scale (ADPKD-IS), ADPKD Pain and Discomfort Scale (ADPKD-PDS), and ADPKD Urinary Impact Scale (ADPKD-UIS) in participants treated with lixivaptan compared with participants treated with placebo.

The population pharmacokinetics (PopPK) objective of Part 1 was:

- To characterize the pharmacokinetic (PK) profile of lixivaptan utilizing PopPK based on sparse plasma sampling.

The exploratory objectives of Part 1 were:

- To assess the effect of lixivaptan on liver volume (LV) as measured by MRI compared to placebo.
- To evaluate the change from baseline in urine osmolality in participants treated with lixivaptan compared with participants treated with placebo.
- To evaluate the effect of lixivaptan on kidney function as assessed by eGFR using a novel serum creatinine and serum cystatin C-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation refit without race variable (CKD-EPIcr-cys_R) compared with placebo.

Part 2 (Year 2):

The key objective of Part 2 was:

- To demonstrate the continued efficacy of lixivaptan in the slowing of deterioration in kidney function in participants randomized to lixivaptan in the double-blind phase (Part 1) as measured by the annualized change from baseline (Part 2) in eGFR at the end of the open-label phase (Part 2).

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The key safety objective of Part 2 was:

- To assess the incidence of liver chemistry test abnormalities during the open-label phase.

The secondary objectives of Part 2 were:

- To assess the rate of change (slope) in on-treatment eGFR in Part 2 in participants treated with lixivaptan in Part 1 and Part 2;
- To assess the effect of lixivaptan on TKV as measured by MRI in Part 2 in participants treated with lixivaptan in Part 1 and Part 2.

The secondary safety objective of Part 2 was:

- To assess the non-hepatic safety and tolerability of lixivaptan.

The health outcomes-related objectives of Part 2 were:

- To evaluate medical resource utilization (e.g., medication use/changes; unplanned office visits; urgent care and emergency department usage; and hospitalizations) resulting from clinical events in participants on lixivaptan.
- To evaluate the change in domain scores of the ADPKD-IS, ADPKD-PDS, and ADPKD-UIS.

The PopPK objective of Part 2 was:

- To further characterize the PK profile of lixivaptan utilizing PopPK based on sparse plasma sampling.

The exploratory objectives of Part 2 were:

- To assess the effect of lixivaptan on LV as measured by MRI following 52 weeks of open-label treatment.
- To evaluate the change in urine osmolality.
- To evaluate the effect of lixivaptan on kidney function as assessed by eGFR using the CKD-EPIcr-cys_R equation following 52 weeks of open-label treatment.

METHODOLOGY:

This was a Phase 3 trial consisting of a 2-arm, double-blind, placebo-controlled, randomized phase (Part 1) followed by a single-arm open-label phase (Part 2) to demonstrate the efficacy and safety of lixivaptan in participants with ADPKD. Part 1 of the trial was designed to demonstrate the efficacy of lixivaptan in slowing the decline in kidney function as measured by the difference in change from baseline of eGFR between the lixivaptan-treated and placebo-treated participants. Part 2 of the study was designed to provide confirmation of the durability of this effect. Additionally, both parts of the study were designed to contribute to an understanding of the safety of lixivaptan, particularly any effects on liver chemistry tests. If agreeable to the participant and at the discretion of the Investigator, designated visits could have been done remotely by a home healthcare clinician (HHC) (where available and locally approved by the Competent Authority (CA) and/or IRB/EC). Some remote visits may also have included telehealth (e.g., telemedicine virtual visit, telephone, or video call (without recording)) with the study site, as applicable. Remote visits may also have been conducted by qualified site personnel who had been delegated the authority to carry out the procedures required at remote visits by the Investigator. Those visits were indicated in the Schedule of Procedures – Part 1 and Schedule of Procedures – Part 2.

Due to the Sponsor's commercial re-evaluation of the program, the study was terminated prematurely, i.e., early termination. The reason for early termination was not for efficacy and/or safety reason(s). The planned study design, which was initiated, is presented below followed by the actual status of the study at the time of termination.

Part 1: The study design for Part 1 is shown in Figure 1. Part 1 Study Schematic. In the planned study, approximately 2250 participants with ADPKD were to be screened in order to randomize 1350 participants to lixivaptan or placebo in a 2:1 ratio in Part 1 of this study. After meeting entry criteria during a 3-to-5-week screening period (that could be extended up to 8 weeks to obtain baseline stability of medications), participants entered a 1-week single-blind placebo run-in period (participants did not know the identity of the study drug being administered) to obtain select baseline measurements followed by a 5 to 6 week single-blind dose titration period during which lixivaptan administered twice daily was titrated to the highest tolerated dose. The minimum dose to enter the Double-blind, Randomized Treatment Period was 100 mg BID. Those participants who successfully titrated and tolerated the study drug were then randomized (2:1) to either continue lixivaptan or switch immediately to matching placebo in a double-blind manner. Randomization was stratified for Chronic Kidney Disease (CKD) Stage (CKD 2 versus CKD 3/CKD 4) and Mayo Clinic ADPKD Image Classification (1C, 1D, or 1E). Double-blind treatment was to be continued for 52 weeks after which study drug was to be held, and final eGFR assessments were to be obtained off-treatment during 3 follow-up visits starting on the 8th day after the last dose of double-blind study drug through the 28th day after the last dose of double-blind study drug.

Part 2: The study design for Part 2 is shown in Figure 2. Part 2 Study Schematic. All participants (placebo and lixivaptan-treated) who entered Part 1 were to be continued into Part 2 of the study and treated with the active drug, lixivaptan, unless study drug was previously discontinued for a safety reason, or a participant withdrew consent. Assuming 90% of participants would have completed the Double-Blind Treatment Period (Part 1), approximately 1215 participants were projected to continue into Part 2. At the beginning of Part 2, participants were to start lixivaptan during the Lixivaptan Re-titration Period to re-establish the dose level that was tolerated during Part 1. The dose was to be increased at weekly intervals until the dose level of lixivaptan, or the inferred dose level for participants randomized to placebo treatment, taken at the end of the Double-blind, Randomized Treatment Period in Part 1 was achieved. In order to maintain blinding of the treatment assignment from Part 1, re-titration during Part 2 would continue to be managed by the Interactive Response Technology (IRT) system, i.e., the blind would not have been broken.

Following re-titration, participants were to be continued on lixivaptan therapy for 52 weeks in the Maintenance Treatment Period of Part 2 and were to be assessed at a study visit every 4 weeks. At the end of 52 weeks, study drug was to be held, and final assessments were to be obtained over 3 follow-up visits starting on the 8th day following the last dose of study drug through the 28th day after the last dose of study drug.

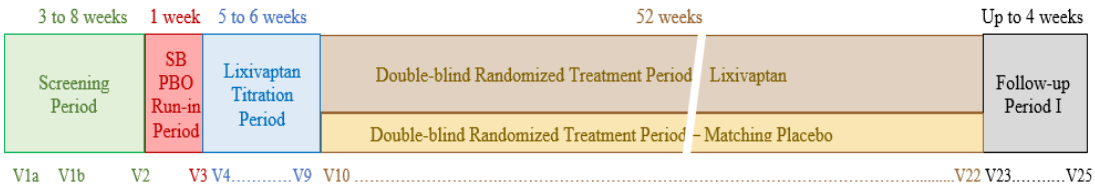
Note: In the event of tolerability issues at any time during the study, dosing could have been decreased or temporarily stopped. If study drug was interrupted for longer than 8 weeks, then study drug treatment would have been permanently discontinued.

At the time of the study early termination, 24 sites had screened a total of 57 participants. Of the 57 participants, 12 enrolled (completed Visit 2) in the study. Of the 12 enrolled participants, 8 received active drug during the titration period and of those 8, 5 participants were randomized.

Due to the staggered nature of regulatory submissions and approvals around the world, two versions of the protocol were active and being used at the time of early termination. The design in Version 3.0 was being used in two countries (Bulgaria and Poland) and Version 1.0 (original protocol) was being used in all other countries. After Version 2.0 was completed and released, but before implementation anywhere in the world, it was realized that additional clarifications and improvements to the text would result in an enhanced protocol. Thus, Version 3.0 was created from Version 2.0, and, in particular, details about the primary endpoint analyses, more typically provided only in the Statistical Analysis Plan, were incorporated into the main body of the study protocol. The major changes from V1.0 to V3.0 are provided below.

1) to increase study power from 85% to 90% resulting in a sample size increase from 1200 randomized to 1350 randomized participants, to meet the mainstream industry standard for powering phase 3 studies, and a direct result of the merging of Palladio into the newly formed Centessa Pharmaceuticals. This was decided before any participant had enrolled into the ACTION study.
2) to update the equation used in the calculation of the primary endpoint from the 2009 CKD-EPI equation to the 2021 CKD-EPIcr_R equation. This updated equation removes the race variable from the calculation of eGFR, per the recent update to this standard. [1]
3) to add exploratory endpoints for eGFR calculated from a combination of serum creatinine and serum cystatin C based on the 2021 CKD-EPIcr-cys_R equation in recognition of the potential for this to be the standard equation in the future. [2]
4) to increase frequency of serum sodium assessments to enhance safety monitoring as recommended by members of the Steering Committee based on the experience in the REPRISE study of tolvaptan.
5) to remove suppression of post-randomization eGFR results to facilitate the Blinded Sample Size Re-estimation process and enhance safety monitoring.
6) to add a benefit/risk paragraph.
7) to incorporate additional guidance about the importance of study participants staying on study drug or continuing in the study off study drug.

Figure 1. Part 1 Study Schematic



SB = Single-Blind, PBO = Placebo

Figure 2. Part 2 Study Schematic

NUMBER OF PATIENTS (PLANNED AND ANALYZED): It was anticipated that approximately 1350 participants would be randomized in the study at approximately 250 sites worldwide. At the time of early termination of the study, 5 participants had been randomized.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Study Indication: Autosomal Dominant Polycystic Kidney Disease

Eligibility criteria were to be assessed at Visits 1a, 1b (if required) and 2. Note: At or prior to Visit 3, eligibility based on mean eGFR (Inclusion criterion #4) from Visit 1a and 2 or Visit 1b and 2 (if Visit 1b was required) and liver chemistry tests (Exclusion criterion #9) from Visit 2 had to be re-confirmed. The following were requirements for entry into the study:

Inclusion Criteria:

1. Male or female, between 18 and 60 years of age (inclusive) at the time of Screening (Visit 1a).
2. Diagnosis of ADPKD by modified Pei criteria:
    - For participants with family history of ADPKD, by ultrasound:
        - 18-39 years: ≥3 cysts, unilateral or bilateral.
        - 40-59 years: ≥2 cysts in each kidney.
        - 60 years: ≥4 cysts in each kidney; or
    - For participants with family history of ADPKD, by computerized tomography (CT) or MRI:
        - 18-40 years: ≥10 cysts in both kidneys; or
    - For participants without family history of ADPKD
        - a minimum of 10 cysts per kidney by any radiologic method and exclusion of other cystic kidney diseases (multiple simple kidney cysts, renal tubular acidosis, cystic dysplasia of the kidney, multicystic kidney, multilocular cysts of the kidney, medullary cystic kidney and acquired cystic disease of the kidney); or
        - genetic diagnosis of ADPKD.
3. At risk for rapid progression of ADPKD as based on the Mayo Clinic ADPKD Image Classification of 1C, 1D, or 1E based on age and height-adjusted TKV as determined by kidney MRI obtained during Screening, where class (class 1 [typical] versus class 2 [atypical]) and TKV are determined by a central imaging vendor.
4. eGFR ≥25 mL/min/1.73 m^2 and ≤90 mL/min/1.73 m^2 based on the mean of 2 eGFR determinations (Visits 1a and 2 or Visits 1b and 2, if Visit 1b is required) calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR creatinine equation refit without the race variable (CKD-EPIcr_R) from serum creatinine values obtained during Screening (Appendix 1 (Section 13.1) of protocol) **Note**: This criterion would preliminarily be reviewed at Visit 2 based on Visit 1a or Visit 1b results (if Visit 1b is required). The criterion would then be re-evaluated no later than Visit 3 when results for Visits 1a and 2 or Visits 1b and 2 were available to confirm that the participant remained eligible for participation.
5. Appropriate control of hypertension for a minimum of 3 weeks including the use of an

angiotensin converting enzyme inhibitor or angiotensin receptor blocker at a stable dose (unless not considered appropriate for the participant) as suggested by the 2021 Kidney Disease Improving Global Outcomes (KDIGO) "Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease," without the use of a diuretic.

6. Body mass index (BMI) between 18 and 40 kg/m^2 (inclusive) at the time of Screening.
7. 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), agree to practice acceptable 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 trial and for 30 days after the last dose of study drug. Birth control methods that can be used during the study include the following:
        - hormonal contraception associated with inhibition of ovulation (i.e., oral, intravaginal, transdermal) progestogen-only hormonal contraception (i.e., oral, injectable, implantable). **Note**: in women with severe polycystic liver disease, contraceptives containing estrogen (and hormone replacement therapy) may be involved in the development and growth of liver cysts and polycystic liver disease progression; the supplemental risk of initiating or continuing estrogen treatment, as well as potential alternative contraceptives for WOCBP will be discussed with the potential participant
        - 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 male condom).
8. Male participants must agree 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 study drug.
9. Have read, understood, and provided written informed consent after the nature of the study has been fully explained and must be willing to comply with protocol requirements and study-related procedures.

Exclusion Criteria:

1. Advanced diabetes (e.g., glycosylated hemoglobin [HgbA1c] >7.5%, and/or glycosuria by dipstick, significant proteinuria [>300 mcg albumin/mg creatinine]), other significant kidney disease, kidney cancer, transplanted kidney, single kidney, kidney surgery within the past 6 months (including cyst drainage or fenestration) or acute kidney injury within 6 months prior to Screening.
2. Clinically significant 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. History of infection with human immunodeficiency virus (HIV) unless the participant is clinically stable and doing well on a non-cytochrome P450 (CYP) interacting anti-retroviral therapy (ART) regimen and the participant has not required more than 2 changes in their ART regimen since treatment inception.
5. History of clinically significant drug or alcohol abuse in the 2 years prior to Screening Visit 1a.
6. Contraindications to or interference with MRI assessments (e.g., ferromagnetic metal prostheses, aneurysm clips, severe claustrophobia, or large abdominal/back tattoos). Investigator should seek MRI safety guidance from the local MRI facility.
7. Any malignancy within 5 years prior to Screening except for basal cell carcinoma successfully treated with local therapy or malignancies that are considered by the Investigator not to affect participant survival (after discussion with the medical monitor).
8. Medical history or findings that preclude safe participation in the trial or participants who are likely to be non-compliant with trial procedures in the opinion of the Investigator or medical monitor.
9. Clinically significant liver disease or impairment or alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin values >1.2 x ULN during Screening. **Note**: This criterion will preliminarily be reviewed at Visit 2 based on Visit 1a and Visit 1b results (if Visit 1b is required). The criterion must be re-evaluated no later than Visit 3 when results for Visit 2 are available.
10. Requirement for ongoing diuretic use.
11. Participants who are currently taking, or are expected to be taking, strong or moderate CYP3A4 or CYP2C8 inhibitors or inducers including regular use of grapefruit juice, Seville oranges, or St. John's wort. If applicable, there should be a 14-day washout of these treatments prior to Visit 2.
12. Prior use of a sodium-glucose cotransporter 2 (SGLT2) inhibitor (e.g., canagliflozin, dapagliflozin, empagliflozin, etc.) within the 2 months prior to Screening Visit 1a or expected need for initiation of treatment with a SGLT2 inhibitor during the study.
13. Prior use of a hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor within the 2 months prior to Screening Visit 1a or expected need for initiation of treatment with a HIF-PH inhibitor during the study.
14. Simvastatin at a total daily dose >10 mg or amlodipine at a total daily dose >5 mg.
15. Prior use of tolvaptan or lixivaptan within the 2 months prior to Screening Visit 1a.
16. Prior use of conivaptan, somatostatin analogs (e.g., lanreotide, pasireotide, octreotide, etc.), metformin (except for diabetes), nicotinamide, bardoxolone, demeclocycline, mTOR kinase inhibitors (e.g., everolimus, sirolimus, etc.), or KetoCitra™ or any beta-hydroxybutyrate (BHB) containing supplements within the 2 months prior to Screening Visit 1a.
17. Participants who have taken any investigational drug or used an investigational device within 30 days, or 5 half-lives, whichever is longer, prior to Screening Visit 1a or plan to participate in an interventional trial during the study.
18. Hypovolemia on physical examination at Screening.
19. Abnormal serum sodium concentration at Screening.
20. Positive test results for hepatitis B surface antigen (HBsAg).
21. Positive test results for hepatitis C (HCV) antibody (Anti-HCV), with the exception of participants for whom the reflex HCV RNA titer test is negative.
22. Known sensitivity or idiosyncratic reaction to lixivaptan and/or its excipients.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

The sponsor (Palladio Biosciences, Inc.) supplied lixivaptan 50 mg capsules and matching placebo for use during the study. Throughout the study, participants were to take 4 capsules BID to mask transitions from one study period to the next. All doses were to be self-administered by participants orally at home with the exception of Visit 3 and any other study visit with scheduled sparse PK sampling, where in-clinic dosing was warranted. Depending on the study period, the treatment arm to which the participant was randomized, and current dose level, the set of 4 capsules were all placebo, all active or a combination of active and placebo capsules. Study drug was assigned via the IRT system throughout the study.

Part 1: During the Placebo Run-in Period, each participant took 4 placebo capsules twice daily (BID) approximately 10 hours apart for 1 week. During the Lixivaptan Titration Period, dosing was started at Level 1 (50 mg BID) and was increased weekly minimally through Level 2 (100 mg BID) and maximally through Level 4 (200 mg BID) according to the dosing schedule shown in Table 1. At the 2 highest dose levels (Level 3 [150 mg BID] and Level 4 [200 mg BID]) where aquaretic effects could be problematic in certain participants, there was an opportunity to reduce the evening (PM) dose to Level 3a (150 mg AM/100 mg PM) for those at Level 3 or Level 4a (200 mg AM/150 mg PM) for those at Level 4. Further dose reductions were allowed as shown in the Lixivaptan Titration Period (Part 1) - Lixivaptan Titration Flowchart. Throughout the study, participants continued to take 4 capsules BID to mask transitions from one study period to the next.

Table 1. Dosing Levels during the Titration Period

Dose Level	AM Dose	PM Dose
1*	50 mg	50 mg
2	100 mg	100 mg
3	150 mg	150 mg
3a**	150 mg	100 mg
4	200 mg	200 mg
4a***	200 mg	150 mg

*Dose Level 1 was for initiation of treatment.
**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).

Once tolerability was achieved, participants remained on that dose for 1 additional week to confirm tolerability (Lixivaptan Titration Period (Part 1) - Lixivaptan Titration Flowchart). As the maximum duration of the Lixivaptan Titration Period was 6 weeks, participants who required a dose reduction at Week 6, as a result of emerging tolerability issues, proceeded to the double-blind period on the newly assigned (reduced) dose level without extension of the titration period. Participants who were unable to tolerate the minimum dose for study entry (100 mg BID/ Level 2) were discontinued from the study. Participants who tolerated their optimized dose were then entered into the Double-blind, Randomized Treatment Period during which time they were randomized 2:1 (lixivaptan: placebo) to continue at the lixivaptan dose level achieved at the end of the Lixivaptan Titration Period or receive matching placebo capsules. During the Double-blind, Randomized Treatment Period, dose could be adjusted downward at the Investigator's discretion if needed to manage non-hepatic side effects. For these participants, the dose level should have been increased back to the dose at the start of the Double-Blind, Randomized Treatment Period once symptoms resolved. The Investigator could temporarily interrupt the study drug, if necessary, to manage acute intercurrent illness, tolerability issues, planned or unplanned surgical procedures or life situations, e.g., airplane travel, etc. In an effort to minimize missing data, wherever practicable, participants who experienced a study drug interruption of 7 or more days were to be

scheduled to have 3 separate serum creatinine samples obtained (minimally 24 hrs. apart between 8 and 28 days after their last dose) for determination of eGFR. Participants who would have required a prolonged interruption due to illness, including COVID-19, or other reasons would have been able to restart the study drug when medically stable and following discussion with the medical monitor and sponsor. Re-establishment of dose was to be required in the event of a prolonged interruption. If study drug was interrupted for longer than 8 weeks, then study drug treatment was to be permanently discontinued.

Part 2: During the Lixivaptan Re-titration Period, dosing was to be started at Level 1 (50 mg BID) and increased weekly until the dose level taken at the end of the Double-blind, Randomized Treatment Period was achieved. This is shown in Table 2. That dose was to be continued for the remainder of Part 2 unless tolerability issues arose, in which case the dose could be lowered. However, periodic attempts were to be made to re-establish the previously achieved dose level from Part 1. If tolerability continued to be problematic, the participant could continue at the lower dose.

Table 2. Dose Titration (Part 2) Based on Dose Achieved at End of Double-blind Randomized Treatment Period in Part 1 for Participants Assigned to Lixivaptan or Placebo in Part 1

Dose Level in Part 1*	Week 1	Week 2	Week 3	Week 4
Level 2 100 mg BID or Placebo	50 mg BID	100 mg BID		
Level 3 150 mg BID or Placebo	50 mg BID	100 mg BID	150 mg BID	
Level 3a 150/100 mg (AM/PM) or Placebo	50 mg BID	100 mg BID	150/100 mg (AM/PM)	
Level 4 200 mg BID or Placebo	50 mg BID	100 mg BID	150 mg BID	200 mg BID
Level 4a 200/150 mg (AM/PM) or Placebo	50 mg BID	100 mg BID	150 mg BID	200/150 mg (AM/PM)

*Participants whose dose was reduced to Level 1 (50 mg BID) during the double-blind phase as a result of tolerability issues or treatment-emergent AEs could continue on that dose during the open-label phase. These participants were initiated dosing at 50mg BID and remained on that dose for 2 weeks during the Re-titration Period and initiated the open-label phase at that dose. Periodic attempts were to be made to re-establish dosing at Level 2 (100 mg BID) during the open-label phase.

Test Product Batch Number: B21036

DURATION OF TREATMENT:

The total duration of participation in the study was to be approximately 123 to 131 weeks (up to 71 weeks in Part 1 and up to 60 weeks in Part 2) depending on the length of Screening (3 to 8 weeks), Titration (5 to 6 weeks), and Re-titration (2 to 4 weeks). Note that the study could be interrupted at any time if safety issues identified by an IDMC potentially compromised the safety of the participants.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:
Placebo Batch Number: B21035

CRITERIA FOR EVALUATION:

Part 1:

Primary Efficacy Endpoint: Annualized change in eGFR calculated from the CKD-EPI equation for serum creatinine from baseline (mean of 3 eGFR determinations obtained during Screening and Placebo Run-in Periods (Visits 1a or 1b (if required), Visit 2, and Visit 3) to final assessment (mean of 3 eGFR determinations obtained during Follow-up Period I or, for participants who discontinued treatment prior to Visit 22, during the Follow-up Period 8 to 28 days following study drug treatment discontinuation).

Key Safety Endpoint: Incidence of serum ALT levels >3 x ULN in participants randomized to lixivaptan compared to those randomized to placebo.

Part 2:

Key Comparison Endpoint: Annualized change in eGFR from baseline (the mean of the 3 eGFR measurements obtained during Follow-up Period I) to the final post-treatment assessment in Part 2 (the mean of the 3 eGFR measurements obtained during Follow-up Period II).

Key Safety Endpoint: Incidence of serum ALT levels > 3 x ULN in participants exposed to lixivaptan in Part 2.

STATISTICAL METHODS:

Sample Size:

Part 1: Based on the results of the REPRISE trial with tolvaptan, it was assumed that the standard deviation for the primary efficacy endpoint, change from baseline to post-treatment follow-up in mean eGFR, was 6.20 mL per minute per 1.73 m^2. Assuming a between-treatment group difference of - 1.40 mL per minute per 1.73 m^2 and a randomization ratio of 2:1 for lixivaptan to placebo, a sample size estimate of 1314 participants (438 placebo participants and 876 lixivaptan participants) was required to achieve 90% power at a significance level of 0.01. In order to compensate for possible dropouts, this estimate had been adjusted up to 1350 participants (450 placebo participants and 900 lixivaptan participants). It was estimated that approximately 2250 participants needed to be screened in order to randomize 1350 participants.

Part 2: This was a convenience sample based on the number of participants who would continue into Part 2. It was estimated that approximately 1350 participants would be randomized in Part 1. All participants except those who discontinued due to an adverse event or withdrew consent were to be continued in Part 2. Approximately 90% (1215) of Part 1 participants were anticipated to continue in Part 2.

Populations for Analysis:

Part 1: The following populations were to be used for analyzing the data from Part 1.

Placebo Run-in Safety Set: The Placebo Run-in Safety Set was to consist of all participants who received at least one dose of placebo during Placebo Run-In Period in Part 1, i.e., all enrolled participants in Part 1.

Lixivaptan Titration Safety Set: The Lixivaptan Titration Safety Set was to consist of all participants who received at least one dose of lixivaptan during Lixivaptan Titration Period in Part 1.

Randomized Safety Set: The Randomized Safety Set was to consist of all participants who received at least one dose of study drug after randomization.

Intent-to-Treat Analysis Set (ITT): The ITT was to consist of all participants who were randomized in Part 1, i.e., all randomized participants in Part 1.

Modified Intent-to-Treat Analysis Set (mITT): The mITT was to consist of all participants in the ITT who received at least one dose of study drug in Part 1. Note that the mITT Analysis Set would consist of the same set of the participants in the Randomized Safety Set.

Primary Efficacy Analysis Set (PEAS): The PEAS was to consist of all participants in the mITT Analysis Set who had both baseline and at least one assessment of eGFR after the treatment was complete or discontinued in Part 1.

Secondary Efficacy Analysis Set (SEAS): The SEAS was to consist of all participants in the mITT Analysis Set who had both baseline and at least one on-treatment assessment of eGFR.

Per-protocol Efficacy Analysis Set (PPAS): The PPAS was to consist of all participants in the PEAS who did not have any protocol deviations that are deemed to potentially impact efficacy.

Part 2: The following populations were to be used for analyzing the data from Part 2.

Part 2 Safety Set (P2SS): The Part 2 Safety Set was to consist of all participants who received at least one dose of lixivaptan in Part 2.

Part 2 Efficacy Analysis Set (P2EAS): The Part 2 Efficacy Analysis Set was to consist of all participants in the Part 2 Safety Set who had at least one assessment of off-treatment eGFR in Part 2.

Parts 1 & 2 (Combined): The following population was to be used for analyzing the data from the study.

Lixivaptan Treated Safety Set (LTSS): The Lixivaptan Treated Safety Set was to consist of all participants who received at least one dose of lixivaptan treatment after randomization during the entire study. This analysis population would be used to summarize safety data during the study for all randomized, lixivaptan-treated participants.

Primary Efficacy Analysis:

Part 1: Baseline eGFR was defined as the mean of the 3 eGFR assessments obtained during the Screening and single-blind, Placebo Run-in Periods. The planned primary efficacy analysis would have utilized the change from this baseline eGFR to the post-treatment follow-up eGFR, annualized by each participant's treatment duration. The post-treatment follow-up eGFR was defined as the mean of 3 eGFR assessments obtained during Follow-up Period I or the equivalent off-therapy eGFR determinations if a participant discontinued study drug earlier.

The estimand corresponding to the primary objective was to be the between-treatment group difference in the change from baseline in eGFR if all the participants in the Primary Efficacy Analysis Set (PEAS) had tolerated and adhered to their treatment for 12 months. Missing data due to randomized participants prematurely discontinued from double-blind treatment were to be handled by annualizing the changes from baseline as follows: each participant's change from baseline was to be divided by the duration in days from the median of the baseline eGFR assessments to the median of the 3 eGFR assessments obtained during the Follow-up Period and then multiplied by 365.25 days.

The primary efficacy endpoint, the annualized change from baseline to post-treatment follow-up in mean eGFR, was to be analyzed by means of an analysis of covariance model with fixed effects for treatment group and the randomization stratification factors and the baseline eGFR as a covariate.

The primary efficacy analysis was to be performed at the 1% level of significance ($P<.01$).

Key Comparison:

Key Comparison Analysis:

Part 2: Baseline eGFR was defined as the mean of the 3 eGFR assessments obtained during Follow-up Period I.

Descriptive statistics were to be presented for the mean of the annualized changes from this baseline to the mean of the 3 eGFR measurements during Follow-up Period II for participants in the Part 2 Efficacy Analysis Set (P2EAS). This was to be compared by descriptive statistics to the corresponding annualized change in eGFR for Part 1 for the same analysis set.

Safety:

Key Safety – Liver Safety Analysis:

Part 1 and 2: Incidence of serum ALT levels >3 x ULN was to be summarized by treatment group in Part 1 and for all participants in Part 2.

Additional Safety Analyses:

Part 1: All safety analyses were to be summarized for the following:

• Single-Blind Placebo Run-in Period for the Placebo Run-in Safety Set

• Lixivaptan Titration Period for the Lixivaptan Titration Safety Set

• The Randomized, Double-blind Treatment and Follow-up Periods for the Randomized Safety Set

Treatment-emergent adverse events, clinical laboratory data, 12-lead ECGs, and vital signs findings were to be analyzed using appropriate descriptive statistics by treatment group. Potentially clinically significant results in clinical laboratory tests, 12-lead ECGs, and vital signs identified using prospectively defined criteria, including criteria for liver enzyme elevations, were also to be summarized by treatment group.

Part 2: Safety analyses were to be performed for the Part 2 Safety Set (P2SS) based on TEAEs, clinical laboratory data, 12-lead ECGs, and vital signs findings using appropriate descriptive statistics overall and by treatment groups from Part 1. Potentially clinically significant results in clinical laboratory tests, 12-lead ECGs, and vital signs identified using prospectively defined criteria, including criteria for liver enzyme elevations, were also to be summarized overall and by treatment group from Part 1.

Parts 1 & 2 (Combined): Adverse events of special interest involving the liver and TEAEs observed during the study were also to be summarized for the Lixivaptan Treated Safety Set (LTSS).

Due to the limited number of enrolled participants at the time of study termination, safety data were summarized in tabular format for treatment-emergent adverse events and ECG results during the lixivaptan titration period in the Lixivaptan Titration Set and during the randomized period in the Randomized Safety Set. Safety and efficacy data are provided as listings.

SUMMARY –CONCLUSIONS:

Disposition of Participants:

Table 3 summarizes the disposition of participants.

A total of 57 participants were screened for eligibility in the study of which 12 participants were enrolled. Of the 12 enrolled participants, four (4) participants failed during the Placebo Run-in Period and eight (8) participants were entered into the Lixivaptan Titration Period. Five participants of the Lixivaptan Titration Set were randomized into the lixivaptan group (n=4) and the placebo group (n=1). The study was discontinued early in all (100%) the participants. None of the participants completed the study.

Of 5 randomized participants, all of them were early terminated from the study. Reasons for early termination from the study included sponsor termination of study (lixivaptan group: n=3, 75% and placebo group: n=1, 100%) and withdrawal of participant consent (lixivaptan group: n=1, 25%).

Table 3. Disposition of Participants

Variable Category	Lixivaptan	Placebo	Total
Screened for Eligibility			57
Screen Failure			45
Enrolled [1]			12
Lixivaptan Titration Set [2]			8
Randomized	4 (100%)	1 (100%)	5 (100%)
Completed Study	0	0	0
Discontinued Early	4 (100%)	1 (100%)	5 (100%)
Reason for Early Termination			
Adverse Event	0	0	0
Death	0	0	0
Investigator or Sponsor Decision	0	0	0
Lack of Efficacy	0	0	0
Lost to Follow-Up	0	0	0
Non-Compliance with Study Drug	0	0	0
Site Terminated by Sponsor	0	0	0
Protocol Deviation	0	0	0
Pregnancy	0	0	0
Sponsor Termination of Study	3 (75.0%)	1 (100%)	4 (80.0%)
Participant Withdrew Consent	1 (25.0%)	0	1 (20.0%)
Other	0	0	0

Note: Percentages are based on the number of randomized participants by treatment groups and total as presented.
[1] Includes three (3) participants (301-10004-001, 301-10004-003, and 301-10009-001) who entered into the Placebo Run-in Period but failed eligibility criteria (Inclusion #4 [baseline eGFR] or Exclusion #9 [baseline liver chemistry tests]) once final screening laboratory results became available during the Placebo Run-in Period. Also, includes Participant 301-10019-001 who did not enter the Lixivaptan Titration Phase due to study termination
[2] The Lixivaptan Titration Set includes all participants who received any amount of Lixivaptan.
Source: Reference Listing 16.2.1

Demographic and Baseline Characteristics:

A summary of demographic and baseline characteristics for all enrolled participants is presented in Table 4.

The enrolled participants comprised a total of 5 male (41.7%) and 7 female (58.3%) participants. The mean age of the study population was 44.9 (±8.40) years with a median of 43 years.

Mean BMI of the study population was 28.47 (±6.795) kg/m^2 with a median of 29.40 kg/m^2.

Family history of ADPKD was reported in 10 (83.3%) participants which was confirmed by ultrasound (n=4, 40%) or CT/MRI (n=6, 60%). No family history of ADPKD was reported in 2 (16.7%) participants and ADPKD was confirmed through an imaging diagnostic method.

Half of the participants (n=6, 50%) were classified as having Class 1C ADPKD as per the Mayo Clinic ADPKD Image Classification. A majority of participants had Stage 3 CKD (n=5, 41.7%) or Stage 4 CKD (n=2, 16.7%).

The mean time since ADPKD diagnosis was 17.75 (±7.818) years with a median of 20 years.

Table 4. Demographic and Baseline Characteristics - Enrolled Participants

Variable Statistic or Category	Total (N=12)
Age (years) [1]	
n	12
Mean (SD)	44.9 (8.40)
Median	43.0
Min, Max	29, 60
Gender	
Male	5 (41.7%)
Female	7 (58.3%)
Ethnicity	
Hispanic or Latino	1 (8.3%)
Not Hispanic or Latino	11 (91.7%)
Race	
American-Indian or Alaska Native	0
Asian	2 (16.7%)
Black or African-American	1 (8.3%)
Native Hawaiian or Other Pacific Islander	0
White	9 (75.0%)
Other	0
Multiple	0
Height (cm)	
n	12
Mean (SD)	172.2 (13.47)
Median	171.0
Min, Max	155, 198
Weight (kg)	
n	12
Mean (SD)	86.5 (30.88)

Table 4. (contd.) Demographic and Baseline Characteristics – Enrolled Participants

Variable Statistic or Category	Total (N=12)
Median	77.5
Min, Max	48, 148
BMI (kg/m^2)	
n	12
Mean (SD)	28.47 (6.795)
Median	29.40
Min, Max	18.6, 39.8
Family History of ADPKD	
Yes	10 (83.3%)
No	2 (16.7%)
ADPKD Diagnostic Method with Family History of ADPKD	
Ultrasound	4 (40.0%)
CT or MRI	6 (60.0%)
ADPKD Diagnostic Method with no Family History of ADPKD	
Imaging	2 (100%)
Genetic Analysis	0
Mayo Clinic ADPKD Classification	
Class 1A	0
Class 1B	0
Class 1C	6 (50.0%)
Class 1D	3 (25.0%)
Class 1E	3 (25.0%)
Not Reported	0
CKD Stage	
Stage 1	2 (16.7%)
Stage 2	3 (25.0%)
Stage 3	5 (41.7%)
Stage 4	2 (16.7%)
Stage 5	0
Not Reported	0
Time Since ADPKD Diagnosis (years) [2]	
n	12
Mean (SD)	17.75 (7.818)
Median	20.00
Min, Max	2.0, 26.0

Abbreviations: ADPKD = autosomal dominant polycystic kidney disease; CKD = chronic kidney disease; SD = standard deviation.
[1] Age as reported on the CRF.
[2] Time since diagnosis (years) is defined as [Year of ICF Signed] – [Year of ADPKD Diagnosis] + 1.
Source: Reference Listings 16.2.3.1, 16.2.3.3 and 16.2.12

EFFICACY RESULTS:

Efficacy data were not analyzed as only 5 participants were randomized, and all 5 participants were prematurely terminated from the study by the sponsor less than 1 month following randomization. One month after randomization was the first scheduled post-randomization visit during which efficacy parameters would have been collected.

SAFETY RESULTS:

Although all adverse events reported after signing the informed consent were captured during the study, only adverse events after at least one dose of lixivaptan (during Lixivaptan Titration Period) and after Randomization are reported in this synoptic CSR.

Adverse Events during Lixivaptan Titration Period

Table 5 summarizes the TEAEs during the Lixivaptan Titration Period in participants (n=8) that received at least one dose of lixivaptan. Note that the summary of Adverse Events tables (Tables 5 and 7) summarizes events per category (severity and causality) and participants per category (severity and causality) but the counts for each are decoupled, i.e., the stated number of events did not necessarily occur in the number of participants that are stated for that category.

A total of 13 TEAEs were observed in 3 (37.5%) participants. Of these, 6 TEAEs were mild in severity and the remaining 7 TEAEs were moderate in severity. Two (25.0%) participants had moderate TEAEs, and 1 (12.5%) participant had only mild TEAEs. No severe TEAEs were reported.

Two events of TEAEs were related to study drug and 11 events were not related to study drug. One (12.5%) participant had TEAEs related to study drug and 2 (15.0%) participants had only TEAEs not related to study drug.

Two events of TEAEs leading to dose reduction of study drug were reported in 1 (12.5%) participant. None of the participants reported TEAEs leading to discontinuation or dose interruption of the study drug. None of the TEAEs led to death and there were no TEAEs of special interest involving the liver in any participant during the Lixivaptan Titration Period.

Table 5. Overall Incidence of Treatment Emergent Adverse Events during Lixivaptan Titration Period

Overall Incidence by Participant Count	Total (N=8)	
	n (%) [1]	Events [2]
Number (%) of Participants Reporting at Least One TEAE		
Any TEAE	3 (37.5%)	13
TEAE by Severity		
Mild	1 (12.5%)	6
Moderate	2 (25.0%)	7
Severe	0	0
TEAE by Relationship to Study Drug [3]		
Related	1 (12.5%)	2
Not Related	2 (25.0%)	11
TEAE Leading to Discontinuation of Study Drug	0	0
TEAE Leading to Dose Interruption of Study Drug	0	0
TEAE Leading to Dose Reduction of Study Drug	1 (12.5%)	2
TEAE Leading to Death	0	0
TEAE of Special Interest Involving the Liver	0	0
Number (%) of Participants Reporting at Least One Serious TEAE		
Any Serious TEAE	0	0

Abbreviation: TEAE = treatment emergent adverse event
[1] Number (%) of participants reporting at least one event.
[2] Total number of events by category.
[3] Participants reporting more than one adverse event are counted only once using the closest relationship to study drug. Not related events include those reported as 'Unlikely Related' or 'Not Related' to study drug; related events include those reported as 'Possibly Related,' 'Probably Related,' or 'Definitely Related' to study drug; missing relationship are considered as 'Definitely Related.'
Note: Participants who reported more than one adverse event (AE) within each category were only counted once at the worst severity. Lixivaptan Titration Period is the time period from dispensation of study drug at Visit 3 until time of Randomization.
Source: Reference Listing 16.2.7

Table 6 summarizes TEAEs by system organ class and preferred term during the Lixivaptan Titration Period.

A total of 13 TEAEs were reported in 3 (37.5%) participants. Nervous system disorders were the most frequently reported TEAEs which included 4 events of headache in 1 participant (12.5%). Two events of gastrointestinal disorders in 1 participant (12.5%) included 1 event of abdominal distension in this participant (12.5%) and 1 event of diarrhea in the same participant (12.5%). Renal and urinary disorders (n=2, 25.0%) included 1 event each of polyuria in 1 participant (n=1, 12.5%) and renal cyst rupture in 1 participant (n=1, 12.5%). Hypertension was reported in 2 (25%) participants. The other TEAEs included nasopharyngitis (n=1, 12.5%), influenza A virus test positive (n=1, 12.5%) and polydipsia (n=1, 12.5%).

Table 6. Treatment Emergent Adverse Events by System Organ Class and Preferred Term during Lixivaptan Titration Period

System Organ Class Preferred Term	Total (N=8)	
	n (%) [1]	Events [2]
At Least One TEAE	3 (37.5%)	13
Gastrointestinal disorders	1 (12.5%)	2
Abdominal distension	1 (12.5%)	1
Diarrhea	1 (12.5%)	1
Infections and infestations	1 (12.5%)	1
Nasopharyngitis	1 (12.5%)	1
Investigations	1 (12.5%)	1
Influenza A virus test positive	1 (12.5%)	1
Metabolism and nutrition disorders	1 (12.5%)	1
Polydipsia	1 (12.5%)	1
Nervous system disorders	1 (12.5%)	4
Headache	1 (12.5%)	4
Renal and urinary disorders	2 (25.0%)	2
Polyuria	1 (12.5%)	1
Renal cyst ruptured	1 (12.5%)	1
Vascular disorders	2 (25.0%)	2
Hypertension	2 (25.0%)	2

Note: All AEs are coded using MedDRA Version 25.0. At each level of summarization (System Organ Class and Preferred Term), participants who reported more than one adverse event (AE) were only counted once. The Lixivaptan Titration Period is the time period from dispensation of study drug at Visit 3 until time of Randomization.
[1] Number (%) of participants reporting at least one event.
[2] Total number of events by category.
Source: Reference Listing 16.2.7

Other Safety Assessments

No clinically significant changes from baseline or trends were observed in hepatic clinical chemistries (Appendix 16.2.8), non-hepatic clinical chemistries (Appendix 16.2.8), hematology results (Appendix 16.2.8), urinalysis (Appendix16.2.8), or vital signs (Appendix 16.2.9) during the Lixivaptan Titration Period.

Adverse Events After Randomization

Table 7 summarizes the overall incidence of TEAEs after randomization.

A total of 5 participants were randomized into the lixivaptan (N=4) and placebo (N=1) groups. Overall, a total of 4 TEAEs were reported in 2 participants (40%) of which 2 were moderate TEAEs and 2 were mild TEAEs. Of these, 3 TEAEs were related to the study drug and 1 TEAE was not related to study drug. TEAEs of special interest involving the liver were reported in 1 (20%) participant. No severe TEAEs were reported. None of the participants reported TEAEs leading to discontinuation, dose interruption or dose reduction of the study drug. No TEAEs that led to death were reported.

In the lixivaptan (N=4) group, a total of 3 TEAEs were reported in 1 (25.0%) participant of which 2 were mild TEAEs and 1 was a moderate TEAE. Of these, 2 TEAEs were related to the study drug and 1 TEAE was not related to study drug.

In the placebo (N=1) group, 1 TEAE was reported in 1 (100%) participant which was moderate in severity and related to study drug. One non-serious TEAE of special interest involving the liver was reported in 1 (100%) participant.

Table 7. Overall Incidence of Treatment Emergent Adverse Events After Randomization

	Lixivaptan (N=4)		Placebo (N=1)		Total (N=5)	
Overall Incidence by Participant Count	**n (%) [1]**	**Events [2]**	**n (%) [1]**	**Events [2]**	**n (%) [1]**	**Events [2]**
Number (%) of Participants Reporting at Least One TEAE						
Any TEAE	1 (25.0%)	3	1 (100.0%)	1	2 (40.0%)	4
TEAE by Severity						
Mild	0	2	0	0	0	2
Moderate	1 (25.0%)	1	1 (100.0%)	1	2 (40.0%)	2
Severe	0	0	0	0	0	0
TEAE by Relationship to Study Drug [3]						
Related	1 (25.0%)	2	1 (100.0%)	1	2 (40.0%)	3
Not Related	0	1	0	0	0	1
TEAE Leading to Discontinuation of Study Drug	0	0	0	0	0	0
TEAE Leading to Dose Interruption of Study Drug	0	0	0	0	0	0
TEAE Leading to Dose Reduction of Study Drug	0	0	0	0	0	0
TEAE Leading to Death	0	0	0	0	0	0
AE of Special Interest Involving the Liver	0	0	1 (100.0%)	1	1 (20.0%)	1
Number (%) of Participants Reporting at Least One Serious TEAE						
Any Serious TEAE	0	0	0	0	0	0

Abbreviation: AE = adverse event; TEAE = treatment emergent adverse event
[1] Number (%) of participants reporting at least one event.
[2] Total number of events by category.
[3] Participants reporting more than one adverse event are counted only once using the closest relationship to study drug. Not related events includes those reported as 'Unlikely Related' or 'Not Related' to study drug; related events include those reported as 'Possibly Related,' 'Probably Related,' or 'Definitely Related' to study drug; missing relationship are considered as 'Definitely Related.'
Note: Participants who reported more than one adverse event (AE) within each category were only counted once at the worst severity.
Source: Reference Listing 16.2.7

Table 8 summarizes TEAEs by system organ class and preferred term after randomization.

Overall, a total of 4 TEAEs were reported in 2 participants (40%).

In the lixivaptan (N=4) group, a total of 3 TEAEs were reported in 1 (25.0%) participant. These included acute kidney injury (mild severity) and hypotension (moderate severity) and were assessed as possibly related to the study drug by the investigator. The remaining 1 TEAE reported was dry eye (mild severity) and assessed as not related to the study drug by the investigator.

In the placebo (N=1) group, 1 TEAE of increased transaminases (moderate severity) was reported in 1 (100%) participant. This was categorized as a non-serious AE of Special Interest. Further detail is provided below.

Table 8. Treatment Emergent Adverse Events by System Organ Class and Preferred Term after Randomization

System Organ Class Preferred Term	Lixivaptan (N=4)		Placebo (N=1)		Total (N=5)	
	n (%) [1]	Events [2]	n (%) [1]	Events [2]	n (%) [1]	Events [2]
At Least One TEAE	1 (25.0%)	3	1 (100.0%)	1	2 (40.0%)	4
Eye disorders	1 (25.0%)	1	0	0	1 (20.0%)	1
Dry eye	1 (25.0%)	1	0	0	1 (20.0%)	1
Investigations	0	0	1 (100.0%)	1	1 (20.0%)	1
Transaminases increased	0	0	1 (100.0%)	1	1 (20.0%)	1
Renal and urinary disorders	1 (25.0%)	1	0	0	1 (20.0%)	1
Acute kidney injury	1 (25.0%)	1	0	0	1 (20.0%)	1
Vascular disorders	1 (25.0%)	1	0	0	1 (20.0%)	1
Hypotension	1 (25.0%)	1	0	0	1 (20.0%)	1

Note: All AEs are coded using MedDRA Version 25.0. At each level of summarization (System Organ Class and Preferred Term), participants who reported more than one adverse event (AE) were only counted once.
[1] Number (%) of participants reporting at least one event.
[2] Total number of events by category.
Source: Reference Listing 16.2.7

Other Safety Assessments

No clinically significant changes from baseline or trends were observed in non-hepatic clinical chemistries (Appendix 16.2.8), hematology results (Appendix 16.2.8), urinalysis (Appendix 16.2.8), or vital signs (Appendix 16.2.9) after randomization.

Adverse Event of Special Interest (AESI) Involving the Liver

Participant 10009-002, a 45-year-old female at Screening, randomized to the placebo group, with a relevant medical history of hypertension and headache reported 1 TEAE of special interest involving the liver described as elevated transaminases.

During study visit 22 (early termination visit) on 09 June 2022, elevated AST levels of 42 U/L (ref. range: 14-34) and ALT levels of 73 U/L (ref. range: 0-33) were reported. At date of onset of AESI, participant's age was reported as 46 years. Both transaminase levels continued to rise during the subsequent follow-up visits before reaching a peak of 58 U/L (ref. range: 10-35) for AST and 131 U/L [(ref. range: 6-29) (4.5 x ULN)] for ALT on 20 June 2022. No clinical signs and symptoms related to this TEAE were reported. The elevated transaminase levels declined steadily over the next few follow-up visits and reached normal levels at 32 U/L (ref. range: 14-34) for AST on 03 August 2022 and 20 U/L (ref. range: 10-60) for ALT on 14 September 2022. The investigator assessed the event to be resolved on 14 September 2022.

No action was taken with respect to the study drug since it had been discontinued on 03 June 2022 when the study was terminated. The Investigator considered the event of 'Elevated transaminases' to be moderate in intensity, non-serious Adverse Event of Special Interest, and 'probably related' to the study drug. The Sponsor considered the event of 'Elevated transaminases' as non-serious and 'probably related to study drug'.

An independent Hepatic Events Review Committee (HERC) judged the event 'Elevated transaminases' as possibly related (likelihood of 25-49% according to the Drug Induced Liver Injury Network [DILIN] criteria) to the study drug since the baseline enzymes were normal (Appendix 16.2.7). The moderately prolonged resolution of the elevated enzymes (6-8 weeks) was consistent with experience with tolvaptan, a chemically related compound. Thus, although the experience with lixivaptan itself was not sufficient to expect prolonged elevations of transaminases over several months, it was agreed that the tolvaptan experience was relevant and sufficient for this assessment. A detailed narrative of this AESI can be found in Appendix 16.2.10.

ECG Results - Fridericia's formula for QTc (QTcF) Criteria:

The QTcF criteria recorded at baseline and at Visit 9 during the Lixivaptan Titration Period and after Randomization are summarized in Table 9 and Table 10, respectively.

The duration of QTcF was normal and remained unchanged at <450 msec at Visit 9 compared to baseline for 5 (62.5%) participants (n=7) in the Lixivaptan Titration Period. The change from baseline at Visit 9 was <30 msec.

Similarly, the duration of QTcF was normal and remained unchanged at <450 msec at Visit 22 and Visit 25 after randomization compared to baseline for both the lixivaptan (n=4) and placebo (n=1) groups. The changes from baseline in two (2) participants were 30-60 msec at Visit 25 for the lixivaptan group.

There were no clinically significant findings in other ECG parameters (Appendix 16.2.9)

Table 9. ECG Results – QTcF Criteria during Lixivaptan Titration Period – Lixivaptan Titration Participants

Parameter (unit) **Visit** **Statistics**	**Total** **(N=8)**
QTcF (msec)	
Baseline [1]	
< 450 msec	7 (87.5%)
450-480 msec	0
> 480 msec	0
Observed Value at Visit 9	
< 450 msec	5 (62.5%)
450-480 msec	0
> 480 msec	0
Change from Baseline at Visit 9	
< 30 msec	5 (62.5%)
30-60 msec	0
> 60 msec	0

Baseline is defined as the last observation recorded before the first dose of Lixivaptan during the Lixivaptan Titration Period. Lixivaptan Titration Period is the time period from dispensation of study drug at Visit 3 until time of Randomization.
[1] Due to inability to digitize ECG leads from Visit 1a (Baseline) for participant 301-04002-001, a QTcF value could not be determined.
Source: Reference Listing 16.2.10

Table 10. ECG Results – QTcF Criteria after Randomization – Randomized Participants

Parameter (unit) Visit Statistics	Lixivaptan (N=4)	Placebo (N=1)	Total (N=5)
QTcF (msec)			
Baseline			
< 450 msec	4 (100%)	1 (100%)	5 (100%)
450-480 msec	0	0	0
> 480 msec	0	0	0
Observed Value at Visit 9			
< 450 msec	4 (100%)	1 (100%)	5 (100%)
450-480 msec	0	0	0
> 480 msec	0	0	0
Change from Baseline at Visit 9			
< 30 msec	4 (100%)	1 (100%)	5 (100%)
30-60 msec	0	0	0
> 60 msec	0	0	0

Baseline is defined as the last observation recorded before the first dose of Lixivaptan during the Lixivaptan Titration Period.
Source: Reference Listing 16.2.10

Serious Adverse Events:

No serious AEs were reported in any of the participants during the course of the study.

Adverse Events Leading to Discontinuation of the Study Drug:

None of the adverse events led to discontinuation of the study drug.

Deaths:

No deaths were reported.

CONCLUSION:

Due to a commercial re-evaluation of the program by the Sponsor, the study was terminated prematurely, i.e., early termination. The reason for early termination was not for efficacy or for safety reason(s). Due to the limited number of participants enrolled and the limited duration of treatment in the study at the time of study termination, no conclusions regarding safety and/or efficacy can be made. There was one reported AESI involving the liver of elevated ALT and AST levels in one participant in the placebo group which resolved. The participant did not have any clinical signs or symptoms related to the AESI.

DATE OF THE REPORT:

15 November 2022

16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

16.1.2 Sample Case Report Form

16.1.3 List of IECs and IRBs and Representative Written Information for Participant

16.1.3.1 List of IECs and IRBs

16.1.3.2 Representative Written Information for Participant and Sample Consent Forms

16.1.4 List and Description of Investigators and Other Important Study Participants

16.1.5 Signatures of Principal Investigator(s) or Sponsor's Responsible Medical Officer

16.1.6 Listing of Participants Receiving Study Drug from Specific Batches

16.1.7 Randomization Scheme and Codes

16.1.8 Audit Certificates

16.1.9 Documentation of Statistical Methods

16.1.10 Documentation of Inter-laboratory Standardization Methods and Quality Assurance Procedures

16.1.11 Publications Based on the Study

16.1.12 Important Publications Referenced in the Report

16.2 Patient Data Listings

16.2.1 Discontinued Participants

Listing Number	Listing Title
Listing 16.2.1	Participant Disposition – All Participants

16.2.2 Protocol Deviations

Listing Number	Listing Title
Listing 16.2.2	Protocol Deviations Enrolled Participants

16.2.3 Patients Excluded from the Efficacy Analysis

16.2.4 Demographic Data

Listing Number	Listing Title
Listing 16.2.3.1	Demographic and Baseline Information - Enrolled Participants
Listing 16.2.3.2	Medical History - Enrolled Participants
Listing 16.2.3.3	ADPKD Medical History - Enrolled Participants
Listing 16.2.3.4	Prior Medications - Enrolled Participants
Listing 16.2.8.8	Serology Test Results at Screening - Enrolled Participants
Listing 16.2.11	Concomitant Medications - Enrolled Participants
Listing 16.2.12	Body Height, Weight, BMI at Screening - Enrolled Participants

16.2.5 Compliance and/or Drug Concentration Data

Listing Number	Listing Title
Listing 16.2.4	Study Drug Accountability and Dispensation - Enrolled Participants

16.2.6 Individual Efficacy Response Data

Listing Number	Listing Title
Listing 16.2.5.1	eGFR Data - Enrolled Participants
Listing 16.2.5.2	htTKV Volumetric Data - Enrolled Participants
Listing 16.2.6.1	ADPKD-Impact Scale - Enrolled Participants
Listing 16.2.6.2	ADPKD-Pain and Discomfort Scale - Enrolled Participants
Listing 16.2.6.3	ADPKD-Urinary Impact Scale - Enrolled Participants

16.2.7 Adverse Event Listings (each participant)

Listing Number	Listing Title
Listing 16.2.7	Adverse Events - Enrolled Participants
Listing 16.2.8.6	Special Liver Events - Enrolled Participants
Listing 16.2.8.7	HERC DILIN for Special Liver Events - Enrolled Participants

16.2.8 Listings of Individual Laboratory Measurements (by participant)

Listing Number	Listing Title
Listing 16.2.8.1	Hematology Laboratory Evaluations - Enrolled Participants
Listing 16.2.8.2	Hepatic Chemistry Laboratory Evaluations - Enrolled Participants
Listing 16.2.8.3	Non-hepatic Chemistry Laboratory Evaluations - Enrolled Participants
Listing 16.2.8.4	Urinalysis Laboratory Evaluations - Enrolled Participants
Listing 16.2.8.5	Pregnancy Laboratory Evaluations - Enrolled Participants

16.2.9 Listings of Vital Signs and ECG Measurements (by participant)

Listing Number	Listing Title
Listing 16.2.9	Vital Signs Measurements - Enrolled Participants
Listing 16.2.10	ECG Measurements - Enrolled Participants

16.2.10 Safety Narrative - AESI Involving the Liver

16.3 Case Report Forms

16.3.1 CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

16.3.2 Other CRFs Submitted

16.4 Individual Participant Data Listings (US Archival Listings)

1 Delgado C, Baweja M, Crews DC, et al. A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease [published online ahead of print, 2021 Sep 23]. J Am Soc Nephrol. 2021;32(12):2994-3015.

2 Inker LA, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. N Engl J Med 2021; 385:1737-1749