Study Title: A Phase 2, Open-Label, Multi-Center Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Lixivaptan in Subjects With Autosomal Dominant Polycystic Kidney Disease

ClinicalTrials.gov ID: NCT03487913

Statistical Analysis Plan (Non-PK/PD) Version 1.0, dated April 25, 2019

Statistical Analysis Plan for Pharmacokinetics/Pharmacodynamics Version 1.0, dated August 12, 2019

Palladio PA-102 Biostatistics Note to File: Urine osmolality and copeptin sample exclusion due to non-drug related anomaly, dated June 26, 2020

STATISTICAL ANALYSIS PLAN (NON-PK/PD)

PA-102

A Phase 2, Open-Label, Multi-Center Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Lixivaptan in Subjects with Autosomal Dominant Polycystic Kidney Disease

AUTHOR: Lynda Olinger

VERSION NUMBER AND DATE: V1.0, 25 APRIL 2019

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 25APR2019) for Protocol PA-102.

	Name	Signature	Date (DDMMMYYYY)
Author:	Lynda Olinger	*Refer to electronic signature*	
Position:	Statistical Team Lead		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date (DDMMMYYYY)
Approved By:	Neil Shusterman, MD		
Position:	Chief Medical Officer		
Company:	Palladio Biosciences		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
V1.0	25APR2019	Lynda Olinger	Not applicable, first version

TABLE OF CONTENTS

1. INTRODUCTION 8

2. STUDY OBJECTIVES 8

2.1. Primary Objective 8

2.2. Secondary Objectives 9

3. STUDY DESIGN 9

3.1. General Description 9

3.2. Schedule of Events 10

3.3. Changes to Analysis from Protocol 10

4. PLANNED ANALYSES 11

4.1. Data Monitoring Committee (DMC) 11

4.2. Interim Analysis 11

4.3. Final Analysis 11

5. ANALYSIS SETS 11

5.1. All Subjects Enrolled Set 11

5.2. Safety Analysis Set 12

6. GENERAL CONSIDERATIONS 12

6.1. Summary Statistics 12

6.2. Reference Start Date and Study Day 12
6.3. Baseline 13
6.4. Retests, Unscheduled Visits and Early Termination Data 13
6.5. Windowing Conventions 14
6.6. Common Calculations 14
6.7. Software Versions 14
7. STATISTICAL CONSIDERATIONS 14
7.1. Sample Size 14
7.2. Estimands 15
7.3. Missing Data 16
7.4. Examination of Subgroups 16
8. OUTPUT PRESENTATIONS 16
8.1. Treatment Summarization 16
8.2. Precision 17
9. DISPOSITION AND WITHDRAWALS 17
9.1. Protocol Deviations 18
9.1.1. Deviations Related to Study Conduct 18
10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 19
10.1. Derivations 19
11. SURGICAL AND MEDICAL HISTORY 20

12. PRIOR AND CONCOMITANT MEDICATIONS 20

13. STUDY MEDICATION EXPOSURE AND COMPLIANCE 21

13.1. Derivations 21

14. PHARMACOKINETICS ANALYSIS 22

15. PHARMACODYNAMIC ANALYSES 22

16. SAFETY OUTCOMES 22

16.1. Adverse Events 22
16.1.1. Severity 23
16.1.2. Relationship to Study Medication 23
16.1.3. TEAEs Leading to Discontinuation of Study Medication 24
16.1.4. Serious Adverse Events 24

16.2. Deaths 25

16.3. Laboratory Evaluations 25
16.3.1. Laboratory Reference Ranges 26

16.4. ECG Evaluation 26

16.5. Vital Signs 27
16.5.1. Vital Signs Markedly abnormal Criteria 28

16.6. Physical Examination 29

16.7. Other Safety Assessments 29

17. DATA NOT SUMMARIZED OR PRESENTED 30

18. REFERENCES 31

APPENDIX 1.PROGRAMMING CONVENTIONS FOR OUTPUTS 32

Output Conventions 32

Dates & Times 32

Spelling Format 32

Presentation of Treatment Groups 32

Presentation of Visits 33

Presentation of Nominal Times 34

Listings 34

APPENDIX 2.PARTIAL DATE CONVENTIONS 35

Algorithm for Treatment Emergence of Adverse Events: 35

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol PA-102. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 5, dated 21 March 2019.

A separate pharmacokinetics/pharmacodynamics (PK/PD) SAP will be written by IQVIA PK and will describe the analysis and presentation of PK and PD data for Protocol PA-102.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objectives of this study are:

- To characterize the safety and tolerability of lixivaptan following multiple doses in autosomal dominant polycystic kidney disease (ADPKD) subjects with relatively preserved kidney function (chronic kidney disease stage 1 [CKD1] and stage 2 [CKD2]) and moderately impaired renal function [CKD3].
- To characterize the PK profile of lixivaptan and its major metabolites (WAY-141624, WAY-138451, and WAY-138758) following multiple doses of lixivaptan in ADPKD subjects with relatively preserved kidney function (CKD1 and CKD2) and moderately impaired renal function (CKD3).

2.2. SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To characterize the effect of lixivaptan on urine osmolality over a 24-hour period following multiple doses of lixivaptan in ADPKD subjects; and
- To characterize the time course of the pharmacodynamic effect of lixivaptan on urine output, total kidney volume, liver volume, plasma copeptin and serum creatinine in ADPKD subjects.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase 2, open-label, parallel-group, multiple dose study designed to evaluate the PK, pharmacodynamic (PD), safety and tolerability of multiple twice daily (BID) doses of 50 mg and 200 mg lixivaptan in ADPKD subjects with chronic kidney disease in stages CKD1, CKD2 or CKD3. Enrolled subjects will be assigned according to CKD classification to take one of 2 lixivaptan oral dose regimens for 7 days as shown below (Table 1). Each dose regimen includes morning (AM) and evening (PM) oral administration of lixivaptan.

Table 1 Chronic Kidney disease Classification Summary by Cohort and Dose Group

CKD Stage	Cohort	N	eGFR[a]	Dose
CKD1 or CKD2	1	8	eGFR ≥ 60 mL/min/1.73 m^2	200 mg BID
CKD3	2	8	eGFR ≥ 30 to < 60 mL/min/1.73 m^2	200 mg BID
CKD1 or CKD2	3	8	eGFR ≥ 60 mL/min/1.73 m^2	50 mg BID
CKD3	4	8	eGFR ≥ 30 to < 60 mL/min/1.73 m^2	50 mg BID

Abbreviations: CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; BID=twice daily.[a] eGFR is calculated by the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Approximately 32 subjects (or more as necessary to achieve 32 study completers) will be enrolled at approximately 15 sites in the United States (US). Subjects will take one of 2 lixivaptan oral dose regimens for 7 days and will be allocated to one of 4 cohorts depending on CKD status. At least 2 males or females will be included in the 8 subjects assigned to each cohort (i.e. can be up to a 25%/75% split of male/female or 75%/25% split of male/female). The 200 mg BID dose cohorts will be enrolled first.

The study includes a screening period of up to 42 days. Subjects will be confined to the clinical research unit (CRU) on 2 separate occasions, with a total period of confinement of up to 7 days and 5 nights. The first confinement period will last up to 4 days (up to 3 nights), and the second confinement period will last 3 days (2 nights). Subjects will return to the CRU on an outpatient basis on Day 4 and Day 6 in the morning for a trough PK assessment. Except for the AM and PM doses on Days 1, 6 and 7, and the AM doses on Days 2, 4 and 6, all other doses will be self-administered by the subject. Subjects will return on Day 35 (±2) for end of study (EOS) assessments.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 12.2 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

There are no meaningful changes in the analysis plans relative to the study protocol.

4. PLANNED ANALYSES

4.1. DATA MONITORING COMMITTEE (DMC)

There is no DMC for this study requiring statistical outputs.

4.2. INTERIM ANALYSIS

No interim analysis is planned for this study.

4.3. FINAL ANALYSIS

All final, planned analyses of safety and efficacy data identified in this SAP will be performed by IQVIA Biostatistics, following Palladio authorization of this SAP, identification of major protocol deviations requiring analysis exclusions, database lock, and determination of analysis sets.

5. ANALYSIS SETS

5.1. ALL SUBJECTS ENROLLED SET

The all subjects enrolled set will contain all subjects who provide informed consent for this study. Subjects in this population will be used for disposition summaries, and where appropriate, will be analyzed according to cohort allocation. Subjects not allocated to a cohort due to screen failure will be indicated as Not Allocated.

5.2. SAFETY ANALYSIS SET

The safety analysis set will contain all subjects who receive at least one dose of study medication and will be analyzed according to treatment received. This analysis set will be used for the safety analyses and for summarization of baseline/demographic characteristics.

6. GENERAL CONSIDERATIONS

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

6.1. SUMMARY STATISTICS

For categorical variables, the analysis set size (N for sample size and n for available data) and percentage (of available data) for each class of the variable will be presented. Percentages will be based on the number of subjects within the relevant analysis set and/or the number of subjects with data available.

All continuous variables will be summarized using descriptive statistics, including number of non-missing observations (n), mean, standard deviation (SD), median, minimum and maximum values.

6.2. REFERENCE START DATE AND STUDY DAY

Study day will be calculated from the reference start date and will be used to show the start/stop day of assessments and events.

The reference start date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study medication). Study day will be calculated relative to reference start date and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:

  Study Day = (date of event – reference date).

If the event date is partial or missing, the study day and any corresponding durations will be missing in the listings.

6.3. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

Unscheduled measurements will not be included in summary statistics but will contribute to the best/worst case value where required (e.g., shift tables) and assessment of clinical outliers.

In the case of a retest of a scheduled assessment, the last available measurement for that scheduled time (i.e., the retest measurement) will be used for summaries unless flagged as invalid.

Listings will include all scheduled, unscheduled, retest and early discontinuation data.

6.5. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test value (after baseline) – Baseline value

6.7. SOFTWARE VERSIONS

All derivations, statistical analyses, summaries and listings will be generated using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

7. STATISTICAL CONSIDERATIONS

7.1. SAMPLE SIZE

Calculations to determine sample size were performed assuming a CV of 0.30 and 0.41 for lixivaptan maximum concentration in the sampled matrix (ng/mL) (C_{max}) and area under the

concentration-time curve (AUC), respectively. Assuming a lognormal distribution, this implies that the variances for the logarithm of C_{max} and AUC are 0.086 and 0.155, respectively. Under these assumptions and a random sample of 8 observations per cohort, the probability is 0.90 that the point estimate of the population central value (observed geometric mean) for lixivaptan C_{max} and AUC will be within (84.3%, 118.6%) and (79.5%, 125.7%) of the population central value (the median), respectively.

From the perspective of tolerability assessment for multiple dose regimens, for the true population incidence rates of 0.10, 0.20, 0.30, 0.40 and 0.50 for a given AE, the probabilities that the AE would not be observed in a group of 8 subjects administered lixivaptan are given in Table 2:

Table 2 Probability of Not Observing an Adverse Event for Various True Incidence Rates

True Incidence Rate	Probability of Not Observing an AE in Group of 8 Subjects
0.1	0.43
0.2	0.168
0.3	0.058
0.4	0.017
0.5	0.004

7.2. ESTIMANDS

As per ICH E9 (R1), the safety and efficacy estimand for this study is described as follows:

Primary Estimand: The safety and tolerability of lixivaptan following multiple doses in autosomal dominant polycystic kidney disease (ADPKD) subjects.

- Population: Subjects with ADPKD and defined further through appropriate inclusion/exclusion criteria.

- Variable (or endpoint): The evaluation of physical examination findings, vital signs, 12-lead electrocardiograms (ECG), clinical laboratory findings, assessment of adverse events (AE), assessment of aquaretic tolerability.
- Strategy for addressing intercurrent event: Regardless if subject discontinues treatment prematurely.
- Population-level summary: Descriptive differences in safety variables and frequencies of AEs and physical examination findings of the four cohorts.

7.3. MISSING DATA

Missing data will not be imputed but analyzed as missing.

7.4. EXAMINATION OF SUBGROUPS

Subgroup analyses will not be performed for this study.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows the conventions for presentation of data in outputs.

8.1. TREATMENT SUMMARIZATION

In general, data will be presented for each cohort, distinguishing between the different renal groups (CKD1/2 and CKD3) and dosages (50 mg, 200 mg). Data will also be presented for all study subjects combined where appropriate.

8.2. PRECISION

Safety variables (i.e., clinical laboratory values, vital signs, and electrocardiogram [(ECG)] intervals), including derivations thereof, will be reported to the same precision as the source data.

For the reporting of descriptive statistics, SD will be presented to 2 digits more precision than the source data and the mean, median and confidence intervals will be presented to 1 digit more precision than the source data. The minimum and maximum will be presented to the same precision as the source data. Percentages and CV (%) will always be reported to 1 decimal place. P-values, if any, shall be reported to 4 decimal places or as <0.0001.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study. Subject disposition will be tabulated for each cohort and for all subjects overall, with the number of subjects allocated to a cohort, who complete the study, prematurely discontinue, and the reason for early discontinuation presented. A summary of all analysis sets and reasons for exclusion from an analysis set will also be presented. Listings will present dates of completion or early withdrawal and the reason for early discontinuation as well as exclusion from an analysis set and reason for exclusion, if applicable, for each subject.

Listings of inclusion/exclusion criteria responses, protocol deviations and study treatment

administration will be provided.

9.1. PROTOCOL DEVIATIONS

A protocol deviation is defined as an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the Investigational Review Board (IRB) and agreed to by the Investigator.

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, which will be recorded in the subject's source documentation. This information will be provided to IQVIA Biostatistics to determine inclusion/exclusion from analysis sets.

9.1.1. DEVIATIONS RELATED TO STUDY CONDUCT

Protocol deviations will be listed including a classification of minor or major, as determined by clinical staff. A major deviation occurs when there is not adherence to the protocol by the subject or Investigator that results in a significant, additional safety risk to the subject or impacts the ability to utilize the data in analyses. Major deviations can include:

- Not adhering to inclusion or exclusion criteria
- Enrolment of the subject without prior Sponsor approval,
- Intentional overdose
- Non-compliance on multiple occasions with major testing procedures (PK, urine osmolality, magnetic resonance imaging)
- Situations leading to involuntary withdrawal of the subject from the trial (e.g.,

repeatedly missing visits)

- Not adhering to US Food and Drug Administration regulations or International Conference on Harmonisation Guideline for Good Clinical Practice

Major deviations may lead to the subject being withdrawn from the study. All other deviations will be considered minor.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Individual subject demographics and baseline characteristics, including height, weight, body mass index (BMI), CKD history and duration of CKD since initial diagnosis, will be presented in listings. In the situation where the date of diagnosis is partial, duration will be determined according to available information relative to date of informed consent. If date of diagnosis is missing in the listings, duration will also be missing. Age, in years, will be obtained from the eCRF and is relative to date of informed consent.

Demographic characteristics will be summarized by means of descriptive statistics, frequency counts and percentages, and will be tabulated by cohort and for all subjects overall. No statistical testing will be carried out for demographic or other baseline characteristics.

10.1. DERIVATIONS

- Duration of CKD since initial diagnosis of CKD:
  - If full CKD date of diagnosis is available, then:

    Duration since diagnosis of CKD (years) = (Date of Informed Consent – CKD Initial Date of Diagnosis) / 365.25.

- If only month and year of diagnosis is available, then:

  Duration since diagnosis of CKD (years) = (Year/Month of Informed Consent – CKD Initial Year/Month of Diagnosis) / 12.

- If only year of diagnosis is available, then:

  Duration since diagnosis of CKD (years) = (Year of Informed Consent – CKD Initial Year of Diagnosis).

11. SURGICAL AND MEDICAL HISTORY

Surgical and medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and will be listed for the safety analysis set by cohort and subject ID. Changes in health or new symptoms occurring during the screening period will be recorded as medical history.

12. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medication usage will be coded using the most recent WHO Drug Dictionary Version and will be summarized and listed for the safety analysis set by cohort and subject ID.

Prior medications are medications which started and stopped prior to the first dose of study medication. Concomitant medications are medications which were taken during the treatment period and either ended during the treatment period or were ongoing at the end of treatment (EOT). Specifically, concomitant medications:

- Started after the first dose of study medication or

- Started prior to the first dose of study medication and were continued after the first dose of study medication

Prior and concomitant medications started before study medication and those started after first dose of study medication will be flagged in the listing as indicated. No partial start and end dates are permitted for concomitant and prior medications.

13. STUDY MEDICATION EXPOSURE AND COMPLIANCE

Exposure to study medication, expressed as the number of doses administered and total dosage administered, will be presented for each cohort in the safety analysis set by means of descriptive statistics, as described in Section 6.1 . Compliance as a percentage will be summarized by means of descriptive statistics.

Subjects will receive 2 doses of the study drug per day for 7 days, i.e., a total of 14 doses per subject. The total prescribed dosage in this study for cohorts 1 and 2 is 2800 mg (200 mg BID for 7 days). Cohorts 3 and 4 will be prescribed a total dosage of 700 mg (50 mg BID for 7 days).

13.1. DERIVATIONS

Compliance with study medication will be based on the drug dosage administration as recorded in the eCRF and is calculated as follows:

- Compliance with study medication = $\frac{Total\ dosage\ administered}{Total\ prescribed\ dosage}\ x\ 100\%$

14. PHARMACOKINETICS ANALYSIS

See separate document (PK/PD SAP).

15. PHARMACODYNAMIC ANALYSES

See separate document (PK/PD SAP).

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

16.1. ADVERSE EVENTS

Adverse events (AEs) will be coded using the most recent version of MedDRA.

Treatment emergent adverse events (TEAEs) are defined as any event not present before exposure to study drug and subsequently started, or any event already present that worsens in either intensity or frequency, after exposure to study drug. An algorithm for determining whether AE is treatment-emergent if AE start date or AE end date is unknown is described in Appendix 2.

Any AEs and serious adverse events (SAEs) related to study participation (e.g., protocol-mandated intervention) will be recorded from the time the subject signs the informed consent form until the start of study treatment. All other AEs and SAEs will be recorded from

the start of study treatment until exit from the study.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, vital sign measurements), including those that worsen from baseline, deemed to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs. Any safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

16.1.1. SEVERITY

Adverse event severity is classified as mild/moderate/severe/life-threatening/death. TEAEs starting after the first dose of study medication with a missing severity will be classified as missing. If a subject reports a TEAE more than once within that system organ class (SOC)/preferred term (PT), the AE with the worst-case severity will be used in the corresponding severity summaries.

16.1.2. RELATIONSHIP TO STUDY MEDICATION

Relationship to study medication, as indicated by the investigator, is classified as "not related", "unlikely related", "possibly related", "probably related", "definitely related". If the final determination of causality is unknown and the investigator does not know whether the study drug caused the event, then the TEAE will be handled as "possibly related to study drug" for reporting purposes.

A "related" TEAE is defined as a TEAE with a relationship to study medication as "possibly related", "probably related" or "definitely related" to study medication. TEAEs with a missing relationship to study medication will be recorded as "possibly related to study drug". If a

subject reports the same AE more than once within that SOC/PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

An overview of severe and serious related TEAEs, as well as TEAEs leading to discontinuation of study medication, permanent discontinuation from the study and death will be summarized for each cohort and dose. Incidence of TEAEs will also be tabulated per cohort by the following:

- By SOC and PT
- By SOC, PT and severity
- By SOC, PT and relationship to study medication

The tables will include the number and percentage of subjects in each category, as well as the number of events. All AE data will be listed for all subjects with both the investigator's verbatim terms and the MedDRA preferred terms. Listings will also include the SAEs, start and end time and date of AEs, relationship to study drug, severity, action taken for the AEs and outcome of the AE.

16.1.3. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the variable pertaining to "Action taken with drug" on the AE page of the eCRF and listed.

16.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be recorded as "Serious" on the AE page of the eCRF and will be listed.

16.2. DEATHS

A listing of all AEs leading to death will be provided.

16.3. LABORATORY EVALUATIONS

Central laboratory results will be included in the reporting of this study for hematology, clinical chemistry (including liver function) and urinalysis. A list of laboratory assessments to be included in the outputs is included in Table 6-1 of the protocol. Assessment windows for laboratory evaluations are presented in Table 12-2 of the protocol. Presentations will use SI units, as provided by the laboratories.

Protocol-specified clinical laboratory tests will be summarized using descriptive statistics. Clinical laboratory data collected during study conduct which were not required per protocol, such as for special testing to evaluate an AE, will be listed separately and not summarized.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X", in the listings.

The following summaries will be provided for laboratory data by cohort at each scheduled timepoint:

- Actual and change from baseline (descriptive statistics n, mean, SD, median, minimum and maximum for quantitative measurements; frequency and proportion for categorical measurements)
- Shift from baseline (normal, low, high) to last observation on treatment (continuous

variables only)

- Individual data listings of laboratory results, with values outside the laboratory's reference range flagged as low or high. Clinical laboratory reference/normal ranges will be included in the listing.
- For urinalysis, shift tables comparing baseline value to maximum value (using number of subjects with results of negative, trace or positive) for categorical variables
- A listing of serum and urine pregnancy results.

16.3.1. LABORATORY REFERENCE RANGES

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges by the lab vendors and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

16.4. ECG EVALUATION

Results of the ECG assessments will be included in the reporting of this study. Overall evaluation of safety ECGs will be summarized by cohort using descriptive statistics as described in Section 6.1, as well as with frequency counts and percentage of subjects with results classified by the investigator as normal, abnormal – not clinically significant (NCS) and abnormal – clinically significant (CS).

The following ECG parameters will be reported for this study: PR interval, QRS duration, QT

interval (uncorrected), QTcF interval, and heart rate and ventricular rate (beats per minute (bpm)). Values will be obtained directly from the eCRF and no derivations are required. Assessment windows are presented in Table 12-2 Appendix 3 of the Protocol.

The following summaries will be provided for ECG data for each cohort over each scheduled timepoint:

- Actual ECG parameter values (descriptive statistics for quantitative measurements)
- Shift from baseline interpretation to the investigator interpretation at each time point
- Incidence of abnormal criteria (frequency counts and percentage of subjects as normal/abnormal NCS/abnormal CS)
- Listing of subjects' individual ECG results

16.5. VITAL SIGNS

The following vital signs measurements will be reported for this study:

- Sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg)
- Pulse rate (beats/minute)
- Respiratory rate (breaths/min)
- Temperature (^{o}C).

The following summaries will be provided for vital signs data at each scheduled timepoint by cohort for the Safety Analysis set using descriptive statistics:

- Actual and change from baseline
- Incidence of markedly abnormal values

- Shift from baseline to all visits assessed against normal criteria (low, normal, high)

Table 3 Vital Signs Normal Criteria

Variable	Unit	Low	High
SBP	mmHg	< 90 mmHg	> 140 mmHg
DBP	mmHg	< 50 mmHg	> 90 mmHg
Pulse	bpm	< 60 bpm	> 100 bpm
Respiratory rate	breaths/min	< 12 breaths/min	> 20 breaths/min
Body temperature	˚C	< 36.1 ˚C	> 37.2 ˚C

All vital sign data will be listed individually by each subject based on the Safety Analysis set. Assessment windows are presented in Table 12-2 in Appendix 3 of the protocol.

16.5.1. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative vital signs measurements will be identified in accordance with the following predefined criteria:

Table 4 Vital Signs Markedly Abnormal Criteria

Variable	Unit	Low	High
SBP	mmHg	≤ 80 mmHg	≥ 200 mmHg
DBP	mmHg	≤ 50 mmHg	≥ 120 mmHg
Pulse	bpm	≤ 40 bpm	≥ 120 bpm
Respiratory rate	breaths/min	≤ 10 breaths/min	≥ 25 breaths/min
Body temperature	˚C	≤ 35.5 ˚C	≥ 37.7 ˚C

16.6. PHYSICAL EXAMINATION

All physical examination findings, including non-scheduled symptom-directed examination results, will be listed individually for each scheduled timepoint, including specification of any abnormalities observed. Incidences of physical examination results (Normal, Abnormal NCS, Abnormal CS) for every visit, as well as a shift table summarizing the changes in physical examination assessments (Normal, Abnormal NCS, Abnormal CS) from baseline to EOS will be provided, using counts and percentages for each cohort. New abnormalities occurring after administration of study medication will be recorded as adverse events.

16.7. OTHER SAFETY ASSESSMENTS

Tolerability data obtained from the Questionnaire for Tolerability will be listed for all subjects. Frequencies and proportions of responses to questions will be summarized by cohort and

dose.

17. DATA NOT SUMMARIZED OR PRESENTED

Details of admission and discharge from the CRU and follicle-stimulating hormones test results will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

18. REFERENCES

1. A Phase 2, Open-Label, Multi-Center Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Lixivaptan in Subjects with Autosomal Dominant Polycystic Kidney Disease. Palladio Biosciences. Protocol PA-102 Version 5, 21 March 2019.

2. Palladio Biosciences. PA-102 eCRF Version 3, 11 March 2019.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT CONVENTIONS

Outputs will be presented according to the IQVIA Global Biostatistics Standard Output Conventions, which is available upon request.

DATES & TIMES

Depending on data available, dates and times will take the format dd-mmm-yyyy; times will take the format hh:mm:ss; combined dates and times will take the format dd-mmm-yyyyThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment group	Treatment label
CKD1/2 200 mg	Cohort 1
CKD3 200 mg	Cohort 2

CKD1/2 50 mg	Cohort 3
CKD3 50 mg	Cohort 4
Not allocated to a cohort	Not allocated

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Screening
Day -1	D-1
Day 1	D1
…	
Day 7	D7
Day 8	D8
Day 9	D9
Day 10	D10
Day 11	D11
End of Study (Day 35)	EOS

PRESENTATION OF NOMINAL TIMES

For outputs, nominal times will be represented as follows:

Long Name (default)	Short Name
Day 1 (0 hr)	D1_0h
Day 1 (1 hr)	D1_1h
Day 1 (2 hr)	D1_2h
…	…
Day 8 (0 hr)	D8_0h
Day 8 (10 hr)	D8_10h

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Cohort
- Center-Subject ID (note no dash in actual output, e.g. Center 01, Subject 01 is 0101, by earliest enrolled to latest enrolled within the cohort),
- Date (where applicable),
- For listings where subjects not allocated to a cohort are included, these will appear in a category after the cohorts labelled 'Not allocated'.

APPENDIX 2. PARTIAL DATE CONVENTIONS

The only items that may have partial dates are medical history start/end dates, CKD initial diagnosis date and AE start/end dates. All other dates collected in the study should be a complete date with dd-mmm-yyyy format.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that	Known	Not TEAE

START DATE	STOP DATE	ACTION
it cannot be on or after study med start date		
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Assumed TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Assumed TEAE
	Missing	Assumed TEAE

STATISTICAL ANALYSIS PLAN FOR

PHARMACOKINETICS/PHARMACODYNAMICS

PA-102

A Phase 2, Open-Label, Multi-Center Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Lixivaptan in Subjects with Autosomal Dominant Polycystic Kidney Disease

AUTHOR: Andrew Ralya

VERSION NUMBER AND DATE: V1.0, 12 AUG 2019

The data related to the sponsor and study contained in the document are confidential and proprietary to the sponsor.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 12Aug2019) for Protocol PA-102.

	Name	Signature	Date (DDMMMYYYY)
Author:	Andrew Ralya		13Aug2019
Position:	Pharmacokinetics Manager		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
			13Aug2019
Approved By:	Elaine Richardson	Elaine Richardson	
Position:	Vice President, Clinical Operations		
Company:	Palladio Biosciences		
Approved By:	Neil Shusterman, MD		12Aug2019
Position:	Chief Medical Officer		
Company:	Palladio Biosciences		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
V1.0	12AUG2019	Andrew Ralya	N/A

TABLE OF CONTENTS

1. INTRODUCTION 8

2. STUDY OBJECTIVES 8

2.1. Primary Objective 8

2.2. Secondary Objectives 9

3. STUDY DESIGN 9

3.1. General Description 9

3.2. Schedule of Events 10

3.3. Changes to Analysis from Protocol 10

4. PLANNED ANALYSES 10

4.1. Data Monitoring Committee 10

4.2. Interim Analysis 10

4.3. Final Analysis 11

5. ANALYSIS SETS 11

5.1. All Subjects Enrolled Set 11

5.2. Safety Analysis Set 11

5.3. Pharmacokinetics Analysis Set 11

5.4. Pharmacodynamic Analysis Set 12

6. GENERAL CONSIDERATIONS 12

6.1. Summary Statistics 12
6.2. Reference Start Date and Study Day 13
6.3. Baseline 14
6.4. Retests, Unscheduled Visits and Early Termination Data 14
6.5. Windowing Conventions 14
6.6. Common Calculations 15
6.7. Software Versions 15

7. STATISTICAL CONSIDERATIONS 15

7.1. Sample Size 15
7.2. Estimands 16
7.3. Missing Data 17
7.4. Examination of Subgroups 17

8. OUTPUT PRESENTATIONS 18

8.1. Treatment Summarization 18
8.2. Precision 18

9. DISPOSITION AND WITHDRAWALS 19

9.1. Protocol Deviations 19
9.1.1. Deviations Related to Study Conduct 20
9.1.2. Deviations Related to PK and PD Analysis 20

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 21

11. SURGICAL AND MEDICAL HISTORY 21

12. PRIOR AND CONCOMITANT MEDICATIONS 21

13. STUDY MEDICATION EXPOSURE AND COMPLIANCE 21

14. PHARMACOKINETIC ANALYSIS 21

14.1. Plasma Concentration Data 22

14.2. Pharmacokinetic Parameters 23

15. PHARMACODYNAMIC ANALYSIS 33

15.1. Pharmacodynamic Endpoints 33

15.2. Pharmacokinetic-Pharmacodynamic Relationships 35

16. SAFETY OUTCOMES 36

17. DATA NOT SUMMARIZED OR PRESENTED 36

18. REFERENCES 37

APPENDIX 1.PROGRAMMING CONVENTIONS FOR OUTPUTS 38

Output Conventions 38

Dates & Times 38

Spelling Format 38

Presentation of Treatment Groups 38

APPENDIX 2.PARTIAL DATE CONVENTIONS 39

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
AM	morning
AUC	area under the plasma concentration-time curve
$AUC_{(0\text{-}14)}$	area under the plasma concentration-time curve from time 0 until 14 hours post-dose
$AUC_{(0\text{-}inf)}$	area under the plasma concentration-time curve extrapolated to infinity
$AUC_{(0\text{-}last)}$	area under the plasma concentration-time curve from time 0 until the last quantifiable concentration
BID	twice daily
BLQ	below the lower limit of quantification
CKD	chronic kidney disease
CKD1	chronic kidney disease stage 1
CKD2	chronic kidney disease stage 2
CKD3	chronic kidney disease stage 3
CL/F	apparent systemic clearance after extravascular dosing
C_{max}	maximum observed plasma drug concentration
CSR	clinical study report
CV	coefficient of variation
eGFR	estimated glomerular filtration rate
N	sample size
n	number of non-missing observations
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PM	evening
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	terminal elimination phase half-life
t_{max}	time to reach maximum plasma concentration
V_Z/F	apparent volume of distribution after extravascular dosing
λ_Z	apparent terminal elimination rate constant

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of pharmacokinetic (PK) and pharmacodynamic (PD) data for Protocol PA-102. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This statistical analysis plan (SAP) is based on protocol version 5, dated 21 March 2019. The analysis and presentation of the data not related to PK or PD are described in an analysis plan (dated 25 April 2019) referred to as the "Non-PK/PD SAP" in this document.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objectives of this study are:

- To characterize the safety and tolerability of lixivaptan following multiple doses in autosomal dominant polycystic kidney disease (ADPKD) subjects with relatively preserved kidney function (chronic kidney disease stage 1 [CKD1] and stage 2 [CKD2]) and moderately impaired renal function [CKD3].
- To characterize the PK profile of lixivaptan and its major metabolites (WAY-141624, WAY-138451, and WAY-138758) following multiple doses of lixivaptan in ADPKD subjects with relatively preserved kidney function (CKD1 and CKD2) and moderately impaired renal function (CKD3).

2.2. SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To characterize the effect of lixivaptan on urine osmolality over a 24-hour period following multiple doses of lixivaptan in ADPKD subjects.
- To characterize the time course of the pharmacodynamic effect of lixivaptan on urine output, total kidney volume, liver volume, plasma copeptin, and serum creatinine in ADPKD subjects.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase 2, open-label, parallel-group, multiple dose study designed to evaluate the PK, PD, safety and tolerability of multiple twice daily (BID) doses of 50 mg and 200 mg lixivaptan in ADPKD subjects with chronic kidney disease in stages CKD1, CKD2 or CKD3. Enrolled subjects will be assigned according to CKD classification to take one of 2 lixivaptan oral dose regimens for 7 days as shown below (Table 1). Each dose regimen includes morning (AM) and evening (PM) oral administration of lixivaptan.

Table 1 Chronic Kidney disease Classification Summary by Cohort and Dose Group

CKD Stage	Cohort	N	eGFR[a]	Dose
CKD1 or CKD2	1	8	eGFR ≥ 60 mL/min/1.73 m^2	200 mg BID
CKD3	2	8	eGFR ≥ 30 to < 60 mL/min/1.73 m^2	200 mg BID
CKD1 or CKD2	3	8	eGFR ≥ 60 mL/min/1.73 m^2	50 mg BID
CKD3	4	8	eGFR ≥ 30 to < 60 mL/min/1.73 m^2	50 mg BID

Abbreviations: CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; BID=twice daily.[a] eGFR is calculated by the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 12.2 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Some safety and/or PD endpoints were not clearly identified/categorized in the protocol. This SAP clarifies which endpoints are considered to be PD endpoints.

Some minor changes were made to some PK parameter abbreviations and/or definitions.

4. PLANNED ANALYSES

4.1. DATA MONITORING COMMITTEE

There is no Data Monitoring Committee for this study requiring statistical outputs.

4.2. INTERIM ANALYSIS

An interim “dry run” analysis is planned on partial data for this study to aid in pre-programming of databases and programs. However, only the results of the final analysis will be included in the clinical study report (CSR).

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics and PK scientist, following Palladio authorization of this SAP, identification of major protocol deviations/events requiring analysis exclusions, database lock, and determination of analysis sets.

5. ANALYSIS SETS

5.1. ALL SUBJECTS ENROLLED SET

The all subjects enrolled set will contain all subjects who provide informed consent for this study. Subjects in this population will be used for disposition summaries, and where appropriate, will be analyzed according to cohort allocation. Subjects not allocated to a cohort due to screen failure will be indicated as Not Allocated.

5.2. SAFETY ANALYSIS SET

The safety analysis set will contain all subjects who receive at least one dose of study medication and will be analyzed according to treatment received. This analysis set will be used for the safety analyses and for summarization of baseline/demographic characteristics, as well as listings of individual PK and PD data.

5.3. PHARMACOKINETICS ANALYSIS SET

The PK analysis set will consist of all subjects who undergo plasma PK sampling and have

evaluable PK assay results, without protocol deviations or events deemed to affect PK evaluation. This analysis set will be used for the statistical analysis/summarization of PK concentration/parameter data and will be analyzed according to treatment received.

5.4. PHARMACODYNAMIC ANALYSIS SET

The PD analysis set will consist of all subjects who receive study drug and have at least one post-dose assessment of any PD endpoint, without protocol deviations or events deemed to affect PD evaluation. This analysis set will be used for the statistical analysis/summarization of PD data and will be analyzed according to treatment received.

6. GENERAL CONSIDERATIONS

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

6.1. SUMMARY STATISTICS

For categorical variables, the analysis set size (N for sample size and n for number of non-missing observations) and percentage (of the number of non-missing observations) for each class of the variable will be presented. Percentages will be based on the number of subjects within the relevant analysis set and/or the number of subjects with non-missing observations.

All continuous variables, except time to reach maximum plasma concentration (t_{max}), will be summarized using descriptive statistics, including N, n, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum values. The CV will not be presented for change from baseline results. Geometric mean and geometric CV will

additionally be included for PK parameters, where applicable. The t_{max} will be summarized using descriptive statistics, including N, n, median, minimum, and maximum only.

For continuous variables, at least 3 (non-missing) observed values for each category will be required for calculation/presentation of descriptive statistics for that category. If n = 2, the 2 values will be presented as minimum and maximum, and no other descriptive statistics will be calculated. If n <2, only n will be reported. If n <2 for all categories for a summary, the summary table/figure may be omitted.

For categorical variables, no minimum number of observed values will be required for calculation/presentation of descriptive statistics (e.g., n and percentage).

6.2. REFERENCE START DATE AND STUDY DAY

Study day will be calculated from the reference start date and will be used to show the start/stop day of assessments and events.

The reference start date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study medication). Study day will be calculated relative to reference start date and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:

  Study Day = (date of event – reference date).

If the event date is partial or missing, the study day and any corresponding durations will be

missing in the listings.

6.3. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to start date of study drug administration (including unscheduled assessments). In the case where the last non-missing measurement and the start date of study drug administration coincide, that measurement will be considered pre-baseline.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

Post-baseline unscheduled measurements will not be included in summary statistics.

In the case of a retest of a scheduled assessment, the last available measurement for that scheduled time (i.e., the retest measurement) will be used for summaries unless flagged as invalid.

Listings will include all scheduled, unscheduled, retest and early discontinuation data.

6.5. WINDOWING CONVENTIONS

See Section 9.1.2 for handling specifications of data collected outside of protocol-specified windows.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test value (after baseline) – Baseline value

6.7. SOFTWARE VERSIONS

All derivations, statistical analyses, summaries, and listings will be generated using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina). Noncompartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 8.0 or higher (Certara, Princeton, New Jersey). Graphics may be prepared using the same versions of SAS or Phoenix WinNonlin.

7. STATISTICAL CONSIDERATIONS

7.1. SAMPLE SIZE

Calculations to determine sample size were performed assuming a CV of 0.30 and 0.41 for lixivaptan maximum observed plasma drug concentration (C_{max}) and area under the plasma concentration-time curve (AUC), respectively. Assuming a lognormal distribution, this implies that the variances for the logarithm of C_{max} and AUC are 0.086 and 0.155, respectively. Under these assumptions and a random sample of 8 observations per cohort, the probability is 0.90 that the point estimate of the population central value (observed geometric mean) for lixivaptan C_{max} and AUC will be within (84.3%, 118.6%) and (79.5%, 125.7%) of the population central value (the median), respectively.

From the perspective of tolerability assessment for multiple dose regimens, for the true

population incidence rates of 0.10, 0.20, 0.30, 0.40 and 0.50 for a given adverse event (AE), the probabilities that the AE would not be observed in a group of 8 subjects administered lixivaptan are given in Table 2:

Table 2 Probability of Not Observing an Adverse Event for Various True Incidence Rates

True Incidence Rate	Probability of Not Observing an AE in Group of 8 Subjects
0.1	0.43
0.2	0.168
0.3	0.058
0.4	0.017
0.5	0.004

7.2. ESTIMANDS

As per International Council for Harmonisation E9 (R1), the estimands for this study are described as follows:

Primary Estimand 1: See Non-PK/PD SAP.

Primary Estimand 2: The PK profile of lixivaptan and its major metabolites (WAY-141624, WAY-138451, WAY-138758) following first and multiple doses of lixivaptan in ADPKD subjects.

- Population: ADPKD subjects with at least one post-dose PK assessment and defined further through appropriate inclusion/exclusion criteria.
- Variables (or endpoints): PK concentrations and parameters (C_{max}, t_{max}, AUC from time 0 until the last quantifiable concentration [$AUC_{(0\text{-last})}$], AUC

extrapolated to infinity [$AUC_{(0\text{-}inf)}$], AUC from time 0 until 14 hours post-dose [$AUC_{(0\text{-}14)}$], terminal elimination phase half-life [$t_{1/2}$], apparent terminal elimination rate constant [λ_z], apparent systemic clearance after extravascular dosing [CL/F; lixivaptan only], and apparent volume of distribution after extravascular dosing [V_z/F; lixivaptan only]).

- Strategy for addressing intercurrent event: Regardless if subject discontinues treatment prematurely.
- Population-level summary: Descriptive differences in PK parameter means of the four cohorts.

7.3. MISSING DATA

Missing data will not be imputed but analyzed as missing, except as specified in Section 14.2.

7.4. EXAMINATION OF SUBGROUPS

Additional exploratory stratification will be made for summarizing some of the PK and/or PD endpoints, including:

- Male versus female (PK only)
- CKD1 versus CKD2 (within Cohorts 1 and 3)

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows the conventions for presentation of data in outputs. The output shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics. Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

8.1. TREATMENT SUMMARIZATION

In general, data will be presented for each cohort, distinguishing between the different renal groups (CKD1/2, CKD1, CKD2, and CKD3) and dosages (50 mg, 200 mg). Data may also be presented for all study subjects combined where appropriate.

8.2. PRECISION

All PK concentrations and PD variables will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimal places the data carry. Elapsed time variables for PK or PD will be reported with 2 decimal places with unit of hours. Derived percentages for PD variables (if any) will be reported in listings with 1 decimal place. Derived PK parameters will be rounded for reporting purposes in by-subject listings. The rounded derived PK data will be considered the source data for the calculation of descriptive statistics. For most derived PK parameters, 3 significant figures will be used as the standard rounding procedure for listings, with the following exceptions:

- Parameters directly derived from source data (e.g., C_{max}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g., t_{max}) will be reported with the same precision as the actual elapsed sampling time value of the source data (specified as 2 decimal places with unit of hours).

For the reporting of descriptive statistics, the mean, geometric mean, median, and SD will be presented to 1 digit more precision than the source data. The minimum and maximum will be presented to the same precision as the source data. Summary percentages (e.g., for categorical variables), CV (%), and geometric CV (%) will always be reported to 1 decimal place.

9. DISPOSITION AND WITHDRAWALS

See Non-PK/PD SAP.

9.1. PROTOCOL DEVIATIONS

A protocol deviation is defined as an unintended or unanticipated departure from the procedures or processes that were approved by the Sponsor and the Investigational Review Board and agreed to by the Investigator.

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, which will be recorded in the subject's source documentation. This information will be provided to IQVIA Biostatistics to determine inclusion/exclusion from analysis sets.

9.1.1. DEVIATIONS RELATED TO STUDY CONDUCT

Major deviations can include, but may not be limited to:

- Deviations related to PK and PD analysis (see Section 9.1.2)

Refer to Non-PK/PD SAP for other examples.

9.1.2. DEVIATIONS RELATED TO PK AND PD ANALYSIS

Protocol deviations or events will also be reviewed by the study pharmacokineticist and biostatistician to identify deviations or events which have the potential to affect the PK or PD results. Deviations resulting in no evaluable PK or PD results for a subject, and thus exclusion from PK or PD analysis set, will be documented as reasons for exclusion from these analysis sets.

Changes to the procedures which may impact the quality of the PK or PD data will be considered major protocol deviations and will be described within the CSR body text. Other events which may impact the quality of the PK or PD data will be described within the CSR body text. These changes or events will include any circumstances that will alter the evaluation of the PK or PD. Examples include, but may not be limited to, vomiting following oral dosing occurring within the time frame of 2 times the median t_{max} (within that cohort, excluding data potentially affected), sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing for the dosing interval for which PK or PD sampling occurs. In the case of a major protocol deviation or event, PK and/or PD data collected during the relevant time period will be listed but excluded from summaries. Other changes to the procedures or events which do not impact the quality of the PK or PD data will not be considered major protocol deviations. Common examples of minor protocol deviations

are a missed sample or minor deviations from sample collection times/windows.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

See Non-PK/PD SAP.

11. SURGICAL AND MEDICAL HISTORY

See Non-PK/PD SAP.

12. PRIOR AND CONCOMITANT MEDICATIONS

See Non-PK/PD SAP.

13. STUDY MEDICATION EXPOSURE AND COMPLIANCE

See Non-PK/PD SAP.

14. PHARMACOKINETIC ANALYSIS

Derivation of the PK parameters from lixivaptan and lixivaptan metabolite (WAY-141624, WAY-138451, and WAY-138758) concentrations will be the responsibility of the clinical pharmacokineticist at IQVIA. The PK and PD summaries, listings, tables, and figures will be the responsibility of the PK/PD biostatistician at IQVIA. Primary PK variables include lixivaptan and lixivaptan metabolite concentrations and parameters.

14.1. PLASMA CONCENTRATION DATA

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A subject listing of all concentration-time data will be presented. Presentation of individual sampling times/concentrations will be based on the Safety Analysis Set.

Lixivaptan and lixivaptan metabolite (WAY-141624, WAY-138451, and WAY-138758) plasma concentrations will be tabulated and summarized by analyte, cohort (equivalent to stratification by renal function/CKD stage and dose), Study Day, dosing interval (AM/PM), and nominal time point using descriptive statistics as described in Section 6.1 and Section 8. Additional summarization will be made with further stratification by gender (male versus female), and, independently, by CKD stage within cohort. Plasma concentrations that are below the lower limit of quantification (BLQ) will be treated as zero for the computation of summary statistics. Concentration summaries will be based on the PK Analysis Set.

The following plots will be presented for the concentration-time data:

- Arithmetic mean concentration versus time data (±SD) for Day 1 and Day 7 will be presented on linear and semi-logarithmic scales, stratified by analyte, cohort (equivalent to stratification by renal function/CKD stage and dose; and further stratified by CKD stage within cohort), Study Day, and dosing interval (AM/PM), based on the PK Analysis Set. Additional figure(s) will be made with further stratification by gender (male versus female).
- Arithmetic mean trough concentration versus nominal Study Day data (±SD) will be presented on a linear scale, stratified by analyte, cohort (equivalent to stratification by renal function/CKD stage and dose; and further stratified by CKD stage within cohort), and dosing interval (AM/PM), based on the PK Analysis Set. Additional figure(s) will be

made with further stratification by gender (male versus female).

- Individual subject concentration versus time data will be graphically presented on linear and semi-logarithmic scales, by analyte, cohort (and CKD stage within cohort), Study Day, and dosing interval (AM/PM), based on the Safety Analysis Set.

14.2. PHARMACOKINETIC PARAMETERS

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters. Any anomalous concentration values (e.g., quantifiable predose concentration for first dose) observed at predose will be identified in the CSR and used for the computation of PK parameters. For first dose, if the anomalous predose concentration is greater than 5% of C_{max} of the profile in that dosing interval, the PK parameters for the given subject/profile will be calculated and reported in the listing but flagged and excluded from statistical summaries and analyses. Predose concentrations will be considered as collected simultaneously with the dose for purpose of PK parameter calculation.

For PK parameter calculations for first dose, predose samples that are missing will be assigned a numerical value of zero. For calculating parameters, no imputation/substitution will be made for missing predose and/or trough concentrations for Day 1 PM or Day 7 AM or PM. For all dosing intervals, any BLQ concentrations (including predose) will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the

collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentration(s) in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

The following PK parameters (

Table 3) will be estimated for lixivaptan and lixivaptan metabolites by non-compartmental methods using validated software and actual elapsed time from dosing. See Table 5 for specific Study Days and dosing intervals for which each PK parameters will be calculated. A minimum of 3 quantifiable post-dose concentration-time data points will be required for calculation of PK parameters.

Table 3 Estimation of PK Parameters

Day 1 AM:

PK Parameter	Definition
C_{max}	Maximum observed plasma drug concentration (ng/mL), obtained directly from the observed concentration versus time data.
t_{max}	Time to reach maximum plasma concentration (h), obtained directly from the observed concentration versus time data.
$AUC_{(0\text{-}last)}$	Area under the concentration-time curve from time 0 until the last quantifiable concentration (ng·h/mL), calculated by linear up/log down trapezoidal summation.
$AUC_{(0\text{-}inf)}$	Area under the concentration-time curve from time 0 extrapolated to infinity (ng·h/mL), calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable observed concentration divided by the elimination rate constant: $AUC_{(0\text{-}last)} + C_{last}/\lambda_z$.
λ_z	Apparent terminal elimination rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. The Best Fit method utilized by WinNonlin will be used to identify the terminal linear phase of the concentration-time profile, with visual assessment and adjustment of the selected data points by the PK scientist if warranted. A minimum of 3 data points will be used for determination.
$t_{1/2}$	Apparent terminal elimination phase half-life (h), determined as $\ln 2/\lambda_z$.
CL/F	Apparent systemic clearance after extravascular dosing (L/h), calculated

PK Parameter	Definition
	as (lixivaptan only): • Day 1 AM: dose divided by $AUC_{(0\text{-inf})}$, or • Day 7 AM: dose divided by $AUC_{(0\text{-last})}$.
V_z/F	Apparent volume of distribution following extravascular dosing (L), calculated as CL/F divided by λ_z (lixivaptan only).

Day 1 PM:

PK Parameter	Definition
C_{max}	Maximum observed plasma drug concentration (ng/mL), obtained directly from the observed concentration versus time data.
t_{max}	Time to reach maximum plasma concentration (h), obtained directly from the observed concentration versus time data.
$AUC_{(0\text{-last})}$	Area under the concentration-time curve from time 0 until the last quantifiable concentration (ng·h/mL), calculated by linear up/log down trapezoidal summation.

Day 7 AM:

PK Parameter	Definition
C_{max}	Maximum observed plasma drug concentration (ng/mL), obtained directly from the observed concentration versus time data.
t_{max}	Time to reach maximum plasma concentration (h), obtained directly from the observed concentration versus time data.
$AUC_{(0\text{-last})}$	Area under the concentration-time curve from time 0 until the last quantifiable concentration (ng·h/mL), calculated by linear up/log down trapezoidal summation.
CL/F	Apparent systemic clearance after extravascular dosing (L/h), calculated as (lixivaptan only): • Day 1 AM: dose divided by $AUC_{(0\text{-inf})}$, or • Day 7 AM: dose divided by $AUC_{(0\text{-last})}$.
V_z/F	Apparent volume of distribution following extravascular dosing (L), calculated as CL/F divided by λ_z (lixivaptan only).
RC_{max}	Accumulation ratio for C_{max}, calculated as (lixivaptan only): [C_{max} on Day 7]/[C_{max} on Day 1].
$RAUC_{(0\text{-last})}$	Accumulation ratio for $AUC_{(0\text{-last})}$, calculated as (lixivaptan only): [$AUC_{(0\text{-last})}$ on Day 7]/[$AUC_{(0\text{-last})}$ on Day 1].

Day 7 PM:

PK Parameter	Definition
C_{max}	Maximum observed plasma drug concentration (ng/mL), obtained directly from the observed concentration versus time data.
t_{max}	Time to reach maximum plasma concentration (h), obtained directly from the observed concentration versus time data.
$AUC_{(0\text{-}last)}$	Area under the concentration-time curve from time 0 until the last quantifiable concentration (ng·h/mL), calculated by linear up/log down trapezoidal summation.
$AUC_{(0\text{-}14)}$	Area under the concentration-time curve from time 0 until 14 hours post-dose (ng·h/mL), calculated by linear up/log down trapezoidal summation. Actual elapsed time for the nominal 14-hour sample will be used for the calculation. If the time deviation at 14 hours is larger than ±15.0%, then $AUC_{(0\text{-}14)}$ will only be listed for that profile and excluded from statistics/summaries.
λ_z	Apparent terminal elimination rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. The Best Fit method utilized by WinNonlin will be used to identify the terminal linear phase of the concentration-time profile, with visual assessment and adjustment of the selected data points by the PK scientist if warranted. A minimum of 3 data points will be used for determination.
$t_{1/2}$	Apparent terminal elimination phase half-life (h), determined as $\ln 2/\lambda_z$.
MRC_{max}	Ratio of metabolite C_{max} to parent lixivaptan C_{max}, calculated for all metabolites and corrected for molecular weight of metabolite and parent

PK Parameter	Definition
	as: $(C_{max,m}/C_{max,p})(MW_p/MW_m)$, where $C_{max,m}$ and MW_m are C_{max} and molecular weight of metabolite, respectively, and $C_{max,p}$ and MW_p are C_{max} and molecular weight of parent lixivaptan, respectively. The following molecular weights are to be used in all MR parameter [MRC_{max} and $MRAUC_{(0-14)}$] calculations: • lixivaptan: 473.93 g/mol • WAY-141624: 505.95 g/mol • WAY-138451: 488.92 g/mol • WAY-138758: 426.82 g/mol
$MRAUC_{(0-14)}$	Ratio of metabolite $AUC_{(0-14)}$ to parent lixivaptan $AUC_{(0-14)}$, calculated for all metabolites and corrected for molecular weight of metabolite and parent as: $(AUC_{(0-14),m}/AUC_{(0-14),p})(MW_p/MW_m)$, where $AUC_{(0-14),m}$ and MW_m are $AUC_{(0-14)}$ and molecular weight of metabolite, respectively, and $AUC_{(0-14),p}$ and MW_p are $AUC_{(0-14)}$ and molecular weight of parent lixivaptan, respectively.

The following PK parameters (Table 4) will be calculated for diagnostic purposes, when appropriate, and listed but will not be summarized.

Table 4 Calculation of PK Parameters for Diagnostic Purposes

PK Parameter	Definition
λ_z_low	The starting time point (h) of the time interval of the log-linear regression to determine λ_z.
λ_z_upp	The ending time point (h) of the time interval of the log-linear regression to determine λ_z.
$t_{1/2}$, Interval	The time interval duration (h) of the log-linear regression to determine λ_z, calculated as λ_z_upp − λ_z_low.
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z. A minimum of 3 data points will be used for determination.
Rsq_adj	Adjusted coefficient of determination for calculation of λ_z. If Rsq_adj <0.800, then λ_z and parameters derived from it will be listed but flagged and excluded from summaries.
$\%AUC_{ex}$	Percentage of $AUC_{(0\text{-inf})}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{(0\text{-inf})}\times 100]$. If the $\%AUC_{ex}$ is greater than 30.0% of $AUC_{(0\text{-inf})}$, then $AUC_{(0\text{-inf})}$ will be listed but flagged and excluded from summaries.

Table 5 lists the above non-diagnostic PK parameters to be calculated by Study Day and dosing interval.

Table 5 Calculation of PK Parameters at Specific Study Days and Dosing Intervals

Study Day & Dosing Interval	PK Parameter
Day 1 AM Dose	C_{max}, t_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}inf)}$, λ_z, $t_{1/2}$, CL/F, V_z/F
Day 1 PM Dose	C_{max}, t_{max}, $AUC_{(0\text{-}last)}$
Day 7 AM Dose	C_{max}, t_{max}, $AUC_{(0\text{-}last)}$, CL/F, V_z/F, RC_{max}, $RAUC_{(0\text{-}last)}$
Day 7 PM Dose	C_{max}, t_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}14)}$, λ_z, $t_{1/2}$, MRC_{max}, $MRAUC_{(0\text{-}14)}$

In accordance with molecular formula and formulation for lixivaptan, no dose adjustment calculations will be made for any molecular conversions between administered drug product and analyte measure.

A subject listing of individual PK parameters for lixivaptan and lixivaptan metabolites will be provided. Parameter listings will be based on the Safety Analysis Set. The PK parameters will be summarized by analyte, cohort (renal function/CKD stage/dose), Study Day, and dosing interval (AM/PM) using descriptive statistics as described in Section 6.1 and Section 8. Additional summarization will be made with further stratification by gender (male versus female), and, independently, by CKD stage within cohort. Parameter summaries will be based on the PK Analysis Set.

Scatter plots of individual and geometric mean PK parameters versus cohort will be presented for lixivaptan only, stratified by Study Day and dosing interval (AM/PM), based on the PK Analysis Set. Additional figure(s)/plot(s) will be made with further stratification by gender

(male versus female), and, independently, by CKD stage within cohort. Additional, graphical presentations of PK data may be added if further illustration of the PK results is deemed appropriate.

15. PHARMACODYNAMIC ANALYSIS

15.1. PHARMACODYNAMIC ENDPOINTS

The following are PD endpoints:

- Urine osmolality
- Specific gravity by refractometer
- Specific gravity by dipstick
- (24-hour) urine output
- (24-hour) fluid intake
- Fluid balance
- Total kidney volume (TKV)
- Liver volume (LV)
- Plasma copeptin
- Estimated glomerular filtration rate (eGFR); calculated by the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation presented in Appendix 1 of the protocol.

A listing of all PD sample collection times will be provided. Subject listings of all PD data will be

presented for the observed values and change from baseline, based on the Safety Analysis Set. The observed value and the change from baseline in the PD endpoints will be summarized by cohort (renal function/CKD stage/dose), Study Day, dosing interval, and/or at each scheduled time point, as applicable, using descriptive statistics as described in Section 6.1 and Section 8. Additional summarization will be made with further stratification CKD stage within cohort. Pharmacodynamic summaries will be based on the PD Analysis Set. Any BLQ concentrations will be treated as 1/2 × LLOQ for the computation of change from baseline and descriptive statistics.

Any values after first administration of study drug are regarded as post-baseline values. Except for urine osmolality, the baseline value is the last value observed prior to first administration of study drug. For urine osmolality assessments, the baseline value for each time point after first administration of study drug is the value observed at the corresponding time point on Day -1 (or Day 1 for the AM predose assessment only).

The number and percentage of subjects who show uninterrupted suppression of urine osmolality over 24 hours, defined as spot urine osmolality <300 mOsm/kg at each time point during a 24-hour measurement period, as well as over 14 hours following the PM dose, will be determined for Day -1, Day 1, and Day 7 by dose and by cohort. The above summary will additionally be presented similarly for subjects who show uninterrupted urine osmolality ≤250 mOsm/kg over 24 hours or 14 hours (PM). The 24-hour measurement periods will be calculated as follows:

- For Day -1, from time = 0 on Day -1 until time = 0 (AM predose) on Day 1;
- For Day 1, from time = 1 h on Day 1 until time = 0 (AM predose) on Day 2; and
- For Day 7, from time = 1 h on Day 7 until time = 0 on Day 8

In addition, the number and percentage of subjects with spot urine osmolality <300 mOsm/kg at each time point during the three 24-hour measurement periods (Day -1, Day 1, and Day 7) will be determined by dose and by cohort. The above summary will additionally be presented similarly for subjects who with spot urine osmolality ≤250 mOsm/kg at each time point.

Figure(s) of mean (±SD) urine osmolality versus time by Day (overlaid within plot), cohort, and CKD stage within cohort, will be produced. Figure(s) of mean (±SD) PD endpoint versus Day by cohort and CKD stage within cohort will be produced for urine output, fluid intake, fluid balance, TKV, LV, and plasma copeptin. All the above PD figures will use a linear scale for the PD dependent variable, using the observed values.

15.2. PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIPS

Figures of individual/mean observed and/or change from baseline PD variables versus individual/mean PK endpoint(s) (lixivaptan only) will be produced for urine osmolality, urine output, TKV, LV, plasma copeptin, and eGFR, based on overlapping subjects/data in the PK analysis set and PD analysis set (excluding subjects/data affected by protocol deviations/events). Plot(s) for urine osmolality will use PK concentrations at all nominal time points coinciding with urine osmolality. Plot(s) for plasma copeptin and eGFR will plot Day 2 PD versus Day 1 PK parameter $AUC_{(0\text{-}inf)}$ or $AUC_{(0\text{-}last)}$, depending on appropriateness. An additional plot will show Day 2 plasma copeptin versus Day 1 PK parameter C_{max}. Plot(s) for urine output will plot Day 1 PD versus Day 1 PK parameter $AUC_{(0\text{-}inf)}$ or $AUC_{(0\text{-}last)}$, depending on appropriateness. Plot(s) for eGFR will plot Day 8 PD versus Day 7 PK parameter $AUC_{(0\text{-}14)}$. Plot(s) for urine output, TKV, LV, and plasma copeptin will plot Day 7 PD versus Day 7 PK parameter $AUC_{(0\text{-}14)}$. An additional plot will show Day 7 plasma copeptin versus Day 7 PK parameter C_{max}. Plot(s) will use PK parameters for Day 1 AM or Day 7 PM. All PD versus PK

figures will use a linear scale for the PD dependent variable.

16. SAFETY OUTCOMES

See Non-PK/PD SAP.

17. DATA NOT SUMMARIZED OR PRESENTED

See Non-PK/PD SAP.

18. REFERENCES

1. A Phase 2, Open-Label, Multi-Center Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Lixivaptan in Subjects with Autosomal Dominant Polycystic Kidney Disease. Palladio Biosciences. Protocol PA-102 Version 5, 21 March 2019.

2. Palladio Biosciences. PA-102 eCRF Version 3, 11 March 2019.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT CONVENTIONS

Outputs will be presented according to the IQVIA Global Biostatistics Standard Output Conventions, which is available upon request.

DATES & TIMES

Depending on data available, dates and times will take the format dd-mmm-yyyy; times will take the format hh:mm:ss; combined dates and times will take the format dd-mmm-yyyyThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment group	Treatment label
CKD1/2 200 mg	Cohort 1
CKD3 200 mg	Cohort 2
CKD1/2 50 mg	Cohort 3

Treatment group	Treatment label
CKD3 50 mg	Cohort 4
Not allocated to a cohort	Not allocated

APPENDIX 2. PARTIAL DATE CONVENTIONS

The only items that may have partial dates are medical history start/end dates, CKD initial diagnosis date and AE start/end dates. All other dates collected in the study should be a complete date with dd-mmm-yyyy format.

1.0 INSTRUCTIONS

1.1 Use this form to document project specific file notes to be made part of the permanent study file. This may include some type of process deviation or simply an explanatory note. If the form is used to document process deviations which impact on other functions, ensure that the file note is circulated to those functional groups and the Project Leader.

IQVIA™

Biostatistics File Note

Section A

Customer:	Palladio Biosciences
Project Code:	WYA34000
Protocol Number:	PA-102
Title of Note:	Urine Osmolality and Copeptin sample exclusion due to non-drug related anomaly

Section B

DESCRIPTION:

1) Subject 0101 – Removal of Urine Osmolality and Specific Gravity data from Day -1 and Day 1, re-running all impacted TLFs, and updating CSR.
A serious issue was identified during clinical conduct with the Urine Osmolality/Specific Gravity collection tubes that impacted only subject 0101 enrolled at Site 01. A preservative, tartaric acid, was present in the tubes but shouldn't have been because that adds osmoles to the urine giving an invalid assessment of Urine Osmolality and Specific Gravity. The error was caught after Day 1 but before Day 7. All Urine Osmolality and Specific Gravity samples for subject 0101 only taken on Day -1 and Day 1 were affected. Extensive correspondence and documentation on this matter (including a CAPA from vendor lab Q^2) was performed. Urine Osmolality and Specific Gravity data for the affected samples on Day -1 and Day 1 for this subject, were not supposed to be included in the statistical analyses.

2) Plasma Copeptin in subject 1504 – Re-running all impacted TLFs with and without affected sample and updating CSR.
Subject 1504, enrolled at Site 15, experienced vasovagal syncope 10 minutes before the blood draw of the affected sample resulting in an acute stress response with a compensatory increase in vasopressin to support blood pressure. The true copeptin level in response to the study drug for this subject is not known due to the above-mentioned anomaly. An additional analysis should be performed without this extraordinary copeptin value as this value is non-drug related.

Further action required:

1) Urine Osmolality and Specific Gravity data for subject 0101 at Day -1 and Day 1 will be flagged in analysis ADPD dataset by means of "hardcoding" and excluded from summary tables and mean figures. The data will be included in subject data listings with footnote added for reason of exclusion from summary statistics and mean figures.

2) Plasma Copeptin for subject 1504 at Day 7 will be flagged in analysis ADPD dataset by means of "hardcoding".
The data will be included in subject data listings with a footnote added for reason of exclusion from summary statistics and mean figures.
The data will be included in the original set of summary tables and mean figures.
Additional summary tables and mean figures (only for the affected tables and figures) to be added with the data mentioned above to be excluded.

IQVIA™

Biostatistics File Note

Section C

AUTHOR:

Name:	Muller Heyns	**Signature:**	
Job Title:	Sr. Statistical Programmer	**Date:**	01-Jul-2020

SPONSOR:

Name:	Neil H. Shusterman, MD	**Signature:**	
Job Title:	Chief Medical Officer	**Date:**	26-Jun-2020