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

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Statistical Analysis Plan Version 2.0, dated 24-Sep-2022

Note: a summary of changes implemented from Version 1.0 (dated 03-Aug-2022) is provided in the Revision History.

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

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Revision History

Version/Date	Version name	Section	Changes implemented
Version 1.0/03Aug2022	Final V1.0	NA	NA
Version 2.0/24Sep2022	Final V2.0	7.2	Added the section for potentially clinically Important criteria for laboratory values, vital signs, and electrocardiograms.

List of Abbreviations

Abbreviation	Definition
ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
CSR	clinical study report
ECG	electrocardiogram
eDISH	evaluation of drug-induced serious hepatotoxicity
eGFR	estimated glomerular filtration rate
EoT	end of treatment
ET	early termination
HERC	hepatic events review committee
HHC	home healthcare clinician
ICF	informed consent form
IRT	interactive response technology
SAP	statistical analysis plan
TFLs	tables, figures and listings
ULN	upper limit of normal
WOCBP	women of childbearing potential

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1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol PA-ADPKD-304 Version 2.0 "A Phase 3, Open-label, Roll-over Study to Assess Long-term Safety of Lixivaptan in Participants with Autosomal Dominant Polycystic Kidney Disease Who Completed Study PA-ADPKD-303: The ALERT Study" dated 20May2020 for final analysis.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

All data analyses and generation of TFLs will be performed using SAS version 9.4® or higher.

2. Study Objectives

2.1. Primary Objective

To assess the hepatic safety of lixivaptan with continued dosing.

2.2. Secondary Objectives

The secondary objectives of this study are:

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

3. Study Design

3.1. General Study Design

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

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

all Visit 1 study procedures and will be dispensed lixivaptan treatment to start the Lixivaptan Re-titration Period.

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

Participants will then continue on lixivaptan treatment for up to 104 weeks during the Maintenance Treatment Period and will be assessed at a study visit every 12 weeks where study procedures will include clinical laboratory determinations, including liver chemistry tests. In between quarterly study visits, participants will be required to have blood drawn for liver chemistry determinations every 4 weeks. Where available and approved, visits designated as "laboratory only" may be conducted remotely by a home healthcare clinician (HHC) or by a designated third-party that will process samples for shipment to the central laboratory. Liver chemistry tests may also be drawn at the clinic if that is convenient.

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

3.2. Randomization and Blinding

The study will not be randomized and will be an open-label study.

3.3. Study Treatments and Assessment

The investigational product, lixivaptan capsule, is formulated as a white hard gelatin capsule with a clear band (without markings) containing 50 mg of lixivaptan.

The study drug (lixivaptan capsule) is intended to be taken orally, i.e., to be swallowed whole with water. The capsule should NOT be opened.

During all treatment periods, study drug will be administered BID, with the PM dose administered approximately 10 hours after the AM dose. During the Lixivaptan Re-titration Period, lixivaptan will be started at 100 mg BID for 1 week followed by the final dose taken at the end of the Maintenance Period for another week to access lixivaptan tolerability. Participants whose final dose was 100 mg BID or less in study PA-ADPKD-303, will proceed directly to Visit 3 following one week of re-titration.

Subjects who tolerate their optimized dose will then enter the Maintenance Period during which

time they will continue at the lixivaptan dose level achieved at the end of the Titration Period. During the Maintenance Period, the dose may be adjusted downward at the Investigator's discretion if needed to manage non-hepatic side effects and may also be increased back to the dose achieved at the end of the Titration Period. The Investigator may instruct the subject to hold the study drug for up to 7 days, if necessary, to manage acute intercurrent illness, tolerability issues, surgical procedures or life situations, e.g., airplane travel, etc. Additionally, subjects who have a longer interruption due to illness, including COVID-19, or other reasons may be able to re-start study drug when medically stable after discussion with the medical monitor and sponsor. Temporary or permanent study drug discontinuation for management of abnormal liver chemistry test results is allowed.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Scheduled of Study Assessments in Table 1.

Table 1. Schedule of Procedures

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

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

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

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

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

[b] Participants who meet all eligibility criteria for enrollment at Visit 1 will be assigned lixivaptan at a dose of 100 mg BID for 1 week to start the re-titration period. At Visit 2, the dose of lixivaptan will be increased from 100 mg BID to the final dose taken at the end of the PA-ADPKD-303 Maintenance Period for those participants whose final dose at the end of the lead-in study was greater than 100 mg BID. Participants will continue on the escalated dose for one week before entering the Maintenance Treatment Period. Participants whose final dose in the lead-in study was 100 mg BID (or lower in exceptional cases), will skip Visit 2 and proceed directly to Visit 3/Last Titration Visit and undergo the assessments scheduled for that visit. Dosing will continue for the remainder of the study at this level. However, if there is difficulty with tolerability, the dose may be temporarily reduced. Dosing reductions for participants on Level 2 (100 mg BID) require prior approval from the medical monitor.

[c] During the Follow-up Period, 3 visits will occur to obtain the 3 serum creatinine values for calculation of eGFR. The first visit (V30) will occur on the 8th day (+3 days) after the last dose of lixivaptan treatment and the last visit (V32) will occur on the 28th day (±3 days) after the last dose of lixivaptan treatment. V31 must be scheduled a minimum of 24 hours apart from either V30 or V32 and should occur 12 to 24 days after the last dose of lixivaptan. At the final visit (V32), additional safety and efficacy assessments will be completed as denoted in Table 1.

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

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

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

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

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

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

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

[k] Chemistry blood samples will be collected according to the schedule in Table 1:

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

4. Study Endpoints

4.1. Primary Endpoint

Safety:

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

4.2. Secondary Endpoints

Safety:

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

Efficacy:

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

5. Sample Size and Power

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

6. Analysis Populations

6.1. Enrolled Population

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

6.2. Safety Population

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

6.3. Efficacy Population

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

7. Statistical Considerations and Analyses

7.1. Planned Analyses

Primary Hepatic Safety Analysis:

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

Secondary Hepatic Safety Analyses:

Similarly, descriptive statistics (n, percentage and 95% confidence intervals) will be utilized to present the 2 secondary endpoints: 1) the proportion of participants with serum ALT levels >5 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in the discontinuation of lixivaptan treatment; and 2) the proportion of participants with serum ALT levels >3 × ULN during the Lixivaptan Re-titration or Maintenance Treatment Periods that were assessed by the independent HERC to be at least probably related to lixivaptan and resulted in lixivaptan dose reduction.

Additional Hepatic Safety Analyses:

Proportion of participants who develop any of the following abnormalities during the Lixivaptan Re-titration or Maintenance Treatment Periods:

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

Additional Non-hepatic Safety Analyses:

The following safety variables will be summarized using appropriate descriptive statistics:

Treatment-emergent adverse events, clinical laboratory data, vital signs, and 12-lead ECGs. Potentially clinically significant results in certain clinical laboratory tests, 12-lead ECGs, and vital signs identified using prospectively defined criteria will be also summarized descriptively.

Efficacy Analysis:

Baseline eGFR is defined as the mean of the 3 eGFR assessments obtained during the Screening Period (Visits 25, 26, and 27 of study PA-ADPKD-303.) The endpoint eGFR is defined as the mean of 3 eGFR assessments obtained during the Follow-up Period of this study. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for the change from baseline in annualized eGFR at endpoint.

7.2. Potentially Clinically Important Results of Laboratory Values, Vital signs and Electrocardiograms

The sponsor-defined criteria for potentially clinically important results of clinical laboratory evaluations are given

Table 2.

Table 2: Potentially Clinically Important Criteria (PCI): Laboratory

Lab Test Category	PCI Criteria
Chemistry	Sodium: <132 mmol/L
	Sodium: >149 mmol/L
	Potassium:<2.5 mmol/L
	Potassium: >6.5 mmol/L
	Calcium: <1.62 mmol/L
	Calcium:>3.49 mmol/L
	Uric acid:>715 µmol/L
	Albumin: <25 g/L
	eGFR: Decrease from baseline of ≥25%
	Glucose: ≤2.5 mmol/L
	Glucose: ≥14.0 mmol/L
Hematology	Leukocytes: ≤ 2.5 x 10^9/L
	Leukocytes: ≥ 15.0 x 10^9/L
	Neutrophils: ≤ 1.5 x 10^9/L
	Platelets: ≤ 50.0 x 10^9/L
	Hemoglobin: Decrease from baseline of ≥ 20 g/L
	Hematocrit: Decrease from baseline of ≥ 10% (absolute change)
Urinalysis	Glucose: ≥2+ or ≥500 mg/dL
	RBC/HPF: >10
	Protein: >2+ or >100 mg/dL
	Ketones: > 2 + or >40 mg/dL
	Leukocytes/HPF: >10

Abbreviations: RBC=Red Blood Cell; HPF=high power field.

The sponsor-defined criteria for potentially clinically important results of vital signs are given in Table 3.

Table 3: Potentially Clinically Important Criteria (PCI): Vital Signs

Heart Rate Decrease of ≥20 beats/min or ≤ 40 beats/min
Heart Rate Increase of ≥20 beats/min or ≥ 120 beats/min
Diastolic Blood Pressure Decrease of ≥ 20 mmHg or ≤ 50 mmHg
Diastolic Blood Pressure Increase of ≥ 20 mmHg or ≥ 105 mmHg
Systolic Blood Pressure Decrease of ≥ 25 mmHg or ≤ 90 mmHg
Systolic Blood Pressure Increase of ≥ 25 mmHg or ≥ 180 mmHg
Weight Decrease of ≥ 10%
Weight Increase of ≥ 10%

The sponsor-defined criterion for potentially clinically important (PCI) results of electrocardiograms (ECG) is defined as QTcF value ≥450 msec.

7.3. Study Early Termination and Data Presentations

This study has been early terminated by Sponsor. Due to only a single male participant being enrolled and prematurely terminated in the study, no statistical analyses will be performed and no summary tables will be generated. The following data listings, if applicable, will be produced for the study report:

- Subject Disposition
- Demographic Characteristics
- Baseline Characteristics – eGFR
- Baseline Characteristics - ALT, AST and Total Bilirubin
- Medical History
- Concomitant Procedures
- Prior and Concomitant Medications
- Drug Accountability
- Drug Tolerability/Modification
- Listing of Serum Creatinine and estimated Glomerular Filtration Rate (eGFR)
- Liver Dysfunction Details
- Additional Potential Hepatic Events
- Adverse Events
- Laboratory Test Results – Hematology
- Laboratory Test Results – Chemistry
- Laboratory Test Results - Liver Chemistry
- Laboratory Test Results – Urinalysis
- Additional Potential Hepatic Testing
- Vital Signs Results
- Electrocardiogram (ECG) Results