STATISTICAL ANALYSIS PLAN (SAP)

Investigational Drug:	Patiromer for Oral Suspension
Treatment:	Chronic Kidney Disease and Hyperkalemia
Study Phase:	Phase 2
Study Title:	Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Patiromer for Oral Suspension in Children and Adolescents 2 to < 18 Years of Age with Chronic Kidney Disease and Hyperkalemia
Protocol Number:	RLY5016-206p
Protocol Version:	4.0
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Sponsor:	Relypsa, Inc. 100 Cardinal Way Redwood City, CA 94063, USA [redacted]
SAP Version:	1.0
SAP Version Date:	17 September 2020
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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ARB	Angiotensin II Receptor Blocker
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BID	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Central Laboratory
CBC	Complete Blood Count
CI	Confidence Interval
CKD	Chronic Kidney Disease
C_{max}	Maximum Concentration
Con Meds	Concomitant Medications
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
D	Day
DAIDS	Division of AIDS
DSMC	Data and Safety Monitoring Committee
E	Exclusion
EC	Ethics Committee
ECG	Electrocardiograms
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ET	Early Termination
EUCTD	European Union Clinical Trials Directive 2001/20/EC
F1	Follow-up Visit 1
F2	Follow-up Phone Call
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HF	Heart Failure
HIPAA	Health Information Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IMP	Investigational Medicinal Product

IRB	Institutional Review Board
IWRS	Interactive Web Response System
K^+	Potassium
KDIGO	Kidney Disease Improving Global Outcomes
M	Months
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PD	Pharmacodynamic
QD	Once Daily
RAASi	Renin-Angiotensin Aldosterone System Inhibitors
RBC	Red Blood Cell Count
S	Screening
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMC	Safety Monitoring Committee
TID	Three Times Daily
US	United States
W	Week
WBC	White Blood Cell Count

TABLE OF CONTENTS

1 INTRODUCTION

This document details the planned analyses for Study RLY5016-206p (EMERALD).

Results obtained from the analyses outlined in this document will provide the basis of the study Clinical Study Report (CSR). Statistical rationale and analysis methods specified in this document take precedence over those described in the protocol, should there be any differences.

2 STUDY OBJECTIVES AND STUDY DESIGN

2.1 Study Objectives

2.1.1 Primary Efficacy Objectives

To assess change from baseline in serum potassium levels to Day 14 following administration of different doses of patiromer administered once daily in children 2 – < 18 years of age with chronic kidney disease (CKD) and hyperkalemia.

2.1.2 Safety Objectives

To assess the safety and tolerability of patiromer in children 2 – < 18 years of age with CKD and hyperkalemia.

2.2 Study Design

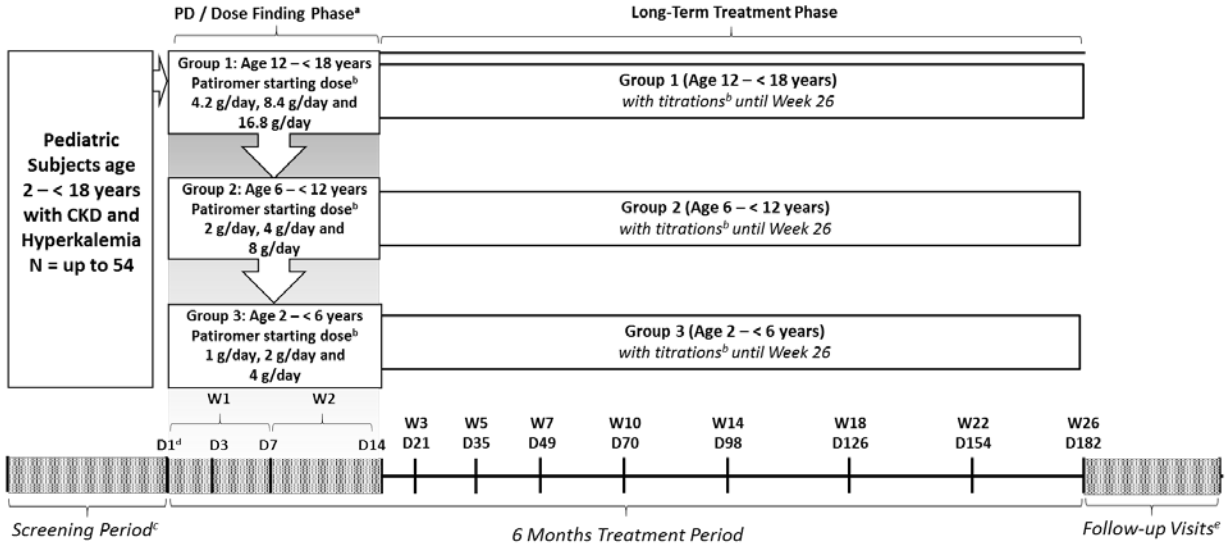
Up to 54 subjects, 2 – < 18 years of age with CKD and hyperkalemia will be enrolled in this open-label, multiple-dose, Phase 2 study. Subjects must be < 18 years of age from the time of study consent until anticipated completion of Day 14 of the study.

The study will include two treatment phases: PD / Dose Finding Phase consisting of the initial 14-day dose finding period followed by an up to 5.5-month Long-Term Treatment Phase for a total study participation duration for individual subjects of up to 6.5 months (see Figure 1). The overall design of the study is presented schematically below.

The study periods comprised of the following (Figure 1):

- Screening Period (up to 7 Days)
- PD / Dose Finding Phase (14 Days)
- Long-Term Treatment Phase (5.5 Months)
- Follow-up Period (14 days after discontinuation of treatment, whether subject completes treatment or discontinues early)

Figure 1: Study Schema



D = day; PD = pharmacodynamic; S = screening; W = week.

[a] Dosing of patiromer will first be initiated in the oldest age cohort 12 – < 18 years of age followed by 6 – < 12 years of age and subsequently 2 – < 6 years of age. The first starting dose tested in each age cohort will be the lowest starting dose.

[b] Dose titration for subjects within a dose group will occur using a protocol specified algorithm (see Section 5.2.1) that is based upon starting dose and targeted to achieve and maintain potassium in the target range (3.8 – 5.0 mEq/L).

[c] Subject's eligibility will be assessed during a Screening Period with up to 2 visits (Screening Visit 1, Screening Visit 2). See Section 3.2.1 for details.

[d] For subjects who meet all other eligibility criteria, Screening Visit 1 or Screening Visit 2 may be converted to the Day 1 Visit (Baseline). See Section 3.2.1 for details.

[e] Follow-up will be 1 and 2 weeks after the last dose of patiromer. Follow-up 1 will be an onsite visit where potassium levels will be measured locally and by central laboratory. Follow-up 2 will be via a phone call unless the investigator requests the subject to return for an onsite visit based on potassium level measured in Follow-up 1.

Note: please see Appendix A and Appendix B for details regarding the study visit window for each scheduled visit including the Follow-up Visits.

2.3 Sample Size Determination

The sample size was selected in a manner that will maximize information for selected starting doses while minimizing exposure of children to ineffective starting doses. The initial number of subjects per age/dose cohort will be 3. When the DSMC agrees that a safe and effective starting dose (i.e., the recommended dose) has been identified for a particular age group, nine additional subjects in the age group will receive the selected starting dose. This will yield a total of 12 subjects per age group. The total sample size for all three age groups could be as low as 36, if the first dose is chosen as safe and effective, and up to 54 if all three dose levels are studied for each age group.

With a sample size of 12 subjects in each age cohort at the identified efficacious and safe starting dose, and assuming a 100% probability of achieving potassium level within the normal range (3.8 – 5.0 mEq/L), the lower bound of the 95% exact confidence interval for achieving this success rate is 73%.

3 INTERIM ANALYSES, FINAL ANALYSIS AND UNBLINDING

This is an open-label multiple dose study to evaluate the pharmacodynamic (PD) effects, safety, and tolerability of patiromer. Subjects and sites study staff will not be blinded to treatment assignment. The data will be periodically evaluated by an independent external data safety monitoring committee (DSMC) and by an internal Relypsa safety committee (SMC). The schedule of the data reviews is detailed in the protocol and in the DSMC charter.

No efficacy interim analysis is planned for this study. The final analysis will be performed after database lock.

4 ANALYSIS SETS

4.1 Efficacy Population

The efficacy population will include all subjects who have taken at least one dose of patiromer.

4.2 Safety Population

The safety population will include all subjects who have taken at least one dose of patiromer.

The safety population and efficacy population are same in this study, so all analyses will be displayed with one population, i.e. safety population.

4.3 Protocol Deviations

All protocol deviations will be recorded in the protocol deviation log. Prior to database lock, all protocol deviations will be compiled.

The following deviations are considered, a priori, to be important protocol deviations:

- Violations of initial informed consent
- Enrolled in violation of the entry criteria
- Administration of a prohibited medication to a study subject potentially affecting the primary and secondary efficacy endpoints
- Study subjects not discontinuing study medication when they met protocol criteria for stopping study treatment
- Dosing with study drug after a study subject's withdrawal from the study

5 ENDPOINTS AND VISIT WINDOWS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

Changes from baseline to Day 14 in serum potassium levels will be summarized by starting dose and age group using descriptive statistics. Baseline potassium will be the last non-missing central laboratory serum potassium value prior to first dose of patiromer. Descriptive statistics include mean, standard deviation, and 95% confidence intervals.

5.1.2 Secondary Efficacy Endpoints

- Proportion of subjects with serum K^+ levels in the range of 3.8 – 5.0 mEq/L at Day 14 (Initial PD / Dose Finding Phase)
- Proportion of subjects with serum K^+ levels in the range of 3.8 – 5.0 mEq/L by visit at any time through Month 6 (Long-Term Treatment Phase)

Proportions and associated exact 95% confidence interval will be presented.

5.1.3 Subgroups

The primary and secondary efficacy analyses may be performed for the following subgroups:

- Sex (male versus female)
- Age (12 – <18 versus 6 – <12 versus 2 – <6 years)
- Race (white versus non-white)

5.2 Safety Endpoints

Safety variables will include:

- All treatment-emergent adverse events (TEAEs)
- Reasons for dosing interruption or discontinuation
- Serious adverse events (SAEs)
- Clinical laboratory test results
- Vital signs
- ECG
- Deaths
- Laboratory safety summaries will include:

- Incidence of potassium (1) < 3.0 mEq/L, (2) < 3.5 mEq/L, (3) ≥ 5.1 mEq/L and (4) ≥ 5.5 mEq/L (measured by central laboratory)
- Incidence of serum magnesium (1) < 1.4 mg/dL (< 0.58 mmol/L), (2) < 1.2 mg/dL (< 0.49 mmol/L) and (3) < 1.0 mg/dL (< 0.41 mmol/L) (central laboratory)
- Calcium levels, phosphate levels, and serum fluoride levels will be assessed based on central laboratory analysis of samples collected at each of the scheduled study visits

5.3 Palatability Assessments

In children ≥ 6 years old, if patiromer is administered onsite, patiromer palatability assessments (taste and overall liking) will be performed on Day 1, using a 5-point facial hedonic scale. For children < 6 years old, parental or authorized legal representative assessment of the subject's acceptance of patiromer on a 5-point agreement/disagreement scale will be performed on Day 14.

5.4 Study Day and Visit Windows

The Study Day for date of first dosing is Day 1. The Study Day for all other study events is defined as follows:

- If a date is prior to the Reference Date, Study Day is defined as [date] - [Reference Date], so the Study Day for the day before date of first dose (typically the first dosing day) is defined as Day -1.

- If a date is on or after the Reference Date, Study Day is defined as [date] - [date of the first dose] +1; hence, the Study Day for the day after first dose is defined as Day 2.

The protocol specified windows for scheduled visits are included in the Schedule of Events (Appendix A and Appendix B).

Unless otherwise specified, analyses by visit will use the visit weeks reported in the database and include results collected at scheduled visits.

Analyses not limited to visits (e.g. incidence of laboratory test values within a given range, and time to event analyses) will include all available values of the variable of interest, irrespective of whether it was collected at a scheduled or unscheduled visit.

For central laboratory data, the visit information from the central laboratory will be used to determine whether a visit is scheduled or unscheduled.

For all analysis variables, unless otherwise specified, baseline is the last non-missing value of the variable on or before the first dose of any study medication.

Modifications to visit schedules may be required due to Coronavirus Disease 2019 (COVID-19). Depending on the scope of changes needed, additional analyses may be undertaken in order to clarify and assess the impact of the modifications to visit schedules. Descriptions of

the additional analyses to be done in relation to COVID-19, if any, will be provided in the SAP prior to database lock.

6 HANDLING OF DROPOUTS AND MISSING DATA

6.1 Missing Information for Adverse Event

For subjects with the missing information for adverse events, the following imputation rules will be applied:

- An adverse event with onset date equivalent to the first dosing date will be considered to be treatment-emergent unless there is evidence to conclude that it is not.
- An adverse event with missing severity will be assigned to the highest severity observed for the subject, among all events with the same preferred term; if there are no other AEs with same preferred term and non-missing severity, the adverse event will be counted as severe.
- An adverse event with missing relationship to study drug will be assigned to possible relationship (i.e. related).

6.2 Missing Dates or Partially Missing Dates

Missing or partially missing dates will be imputed for concomitant medications, procedures and adverse events (AEs). Specific rules for handling missing or partially missing dates are provided in the Appendix C.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 General Considerations and Statistical Methods

For continuous variables, descriptive statistics will include the number of subjects, mean, standard deviation (SD), standard error (SE), median, 25^{th}, 75^{th} percentiles, minimum and maximum.

For categorical variables, descriptive statistics will include frequencies and percentages in each category.

When mean change from baseline is assessed, a subject will be included in the analysis if he/she has a baseline and a post-baseline measurement.

All statistical tests will be conducted at a two-sided alpha level of 0.05 and 95% confidence intervals will be utilized, unless otherwise stated.

All table results, unless otherwise specified, will be displayed by age cohort, starting dose, and overall. For subjects who transition to maintenance hemodialysis or peritoneal dialysis during the study, their data after the start of dialysis will be excluded from summary tables and will be included in listings only.

7.2 Subject Disposition

The number of subjects screened, subjects enrolled, subjects who received at least one dose of study drug, subjects who completed the Day 14 visit, subjects who completed the Week-26 visit, subjects who withdrew from the study before the Week-26, the primary reasons for early study termination will be summarized.

Listings of data supporting subject disposition and the reason for screening failures will be provided.

7.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the ITT and safety population.

The summary of demographic information will include age, gender, race and ethnicity. The summary of patient characteristics at baseline will include, weight, height, and BMI. Baseline medical history will include chronic kidney disease and its etiology, whether patient was on peritoneal dialysis, whether patient ever received a renal transplant, whether patient had diabetes mellitus and its type, , heart failure and its type, ejection fraction percentage, baseline serum potassium and eGFR.

Listings of demographics and baseline characteristics will also be provided.

7.4 Medical History

General medical history will be coded in accordance with the latest MedDRA version and will be summarized by body system (or procedure).

A listing of general medical history will be provided.

7.5 Prior and Concomitant Medications

All prior and concomitant medications will be coded using the latest version of the World Health Organization Drug (WHO Drug) dictionary.

Prior medications are defined as medications with start date before the date of first dose of study drug. Concomitant medications are those taken during the study period and are defined as medications with start date on or before the date of last dose of study drug and end date on or after the date of first dose of study drug, or no end date.

Prior and concomitant medications will be separately summarized by ATC2 class and preferred drug name. Additional summaries may be provided for concomitant medications of interest.

Listings of all prior and concomitant medications will be provided.

7.6 Exposure to Study Drug

The actual prescribed dose of patiromer by cohort, starting dose, and study day will be summarized.

A listing for drug exposure will be provided.

7.7 Treatment Compliance

Treatment compliance for each subject will be estimated and listed separately for the 14-day PD/dose finding period and the long-term treatment phase. Dose compliance will be derived from the total dose of study drug taken by a subject divided by the prescribed total dose over the treatment period for the subject, multiplied by 100.

7.8 Protocol Deviations

The number and percentage of patients with important protocol deviations by category of deviation will be summarized. A listing of important protocol deviations will be provided.

7.9 Efficacy Analyses

7.9.1 Primary Efficacy Analysis

Changes from baseline to Day 14 in serum potassium levels from a central laboratory will be summarized using descriptive statistics. Baseline potassium will be the last non-missing central serum potassium value prior to first dose of patiromer. Descriptive statistics include mean, standard deviation, and 95% confidence intervals.

7.9.2 Secondary Efficacy Analysis

Number and proportion of subjects with central serum potassium levels in the range of 3.8 – 5.0 mEq/L at Day 14 (Initial Pharmacodynamic / Dose Finding Phase) and proportion of subjects with central serum potassium levels in the range of 3.8 – 5.0 mEq/L by visit through Month 6 (Long-Term Treatment Phase) will be presented.

Proportions will be provided along with the 95% confidence intervals, obtained using Exact (Clopper-Pearson) method.

Central serum potassium and mean changes in serum potassium at each scheduled visit will be presented graphically. Central and local laboratory potassium values from serum samples will be included in listings.

7.9.3 Additional Subgroup Analyses

The primary and secondary analyses may be performed for the following subgroups:

- Sex (male versus female)
- Age (12 – <18 versus 6 – <12 versus 2 – <6 years)

- Race (white versus non-white)

7.10 Safety Analyses

7.10.1 Adverse Events

AEs and SAEs will be coded to system organ class (SOC) and preferred term (PT) with the latest available MedDRA. Adverse event analyses will include only treatment-emergent AEs (TEAEs). A TEAE is defined as any AE that newly appeared or worsened in severity following initiation of study drug administration. If the onset date of an AE is missing, the AE will be considered treatment-emergent unless there is evidence to conclude that it is not. AE listings will include all AEs.

The incidence of TEAEs will be summarized by system organ class (SOC), preferred term (PT) and severity. For those TEAEs that occur more than once during the study period, the maximum severity will be used in the summary by severity.

Descriptive statistical summaries (frequencies and percentages) will be provided for the followings:

- Overall summary of number of subjects with: any TEAE; any TEAE related to study drug; any SAE; any SAE related to study drug; any TEAE leading to study drug dose increase, dose reduction, dose interruption; any TEAE leading to study drug discontinuation
- Summary of all TEAEs by SOC, PT and severity
- Summary of TEAEs related to study drug by SOC and PT
- Summaries of TEAEs leading to study drug dose increase, dose reduction, and interruptions by SOC and PT
- Summary of TEAEs leading to early study drug discontinuation by SOC and PT
- Summary of SAEs by SOC, PT, and severity
- Summary of SAEs related to study drug by SOC and PT
- Summaries of TEAEs of special interest (e.g. allergic reactions, gastrointestinal events, renal events)

A listing for all AEs will be provided, including verbatim term, PT, SOC, severity, whether serious, relationship to study drug, onset and end date, action taken, and outcome of event will be provided. A listing of SAEs and TEAEs leading to any study drug modification or discontinuation (increase, reduction, interruption or discontinuation) will also be provided. In addition, listings will be provided for events of special interest.

7.10.2 Death

If there are any deaths, a listing of deaths will be provided.

7.10.3 Clinical Laboratory Tests

For central laboratory test summaries by visit, the central laboratory measurements at scheduled visits will be used if available. The visit name from the central laboratory will be used to determine whether a visit is scheduled or unscheduled.

If a laboratory result from a visit is retested and the central laboratory subsequently determines the original result to be valid, the original result for that visit will be used in analysis, and the second (i.e. 'retested') value will be ignored. Otherwise, if the central laboratory detects an error through the retesting, the retested value will be used in analysis as the measurement for that visit.

The baseline central laboratory value is defined as the last non-missing central laboratory value collected on or before the date of the first dose of study medication.

All serum chemistry, hematology, serum fluoride, and plasma parathyroid hormone level results and change from baseline will be summarized with descriptive statistics at each scheduled visit.

The incidence of laboratory test results in ranges of interest will be summarized. These summaries will include but are not limited to the following:

- Serum potassium < 3.0, < 3.5, < 3.8, > 5.0, and ≥ 5.5 mEq/L
- Serum magnesium < 1.4, < 1.2, and < 1.0 mg/dL
- Serum calcium > 10.2 mg/dL

Laboratory shift tables from baseline to end of dose finding period and baseline to end of treatment will be presented for serum calcium, magnesium and phosphate.

Listings will be provided for all laboratory parameters. Listings will include test results at both scheduled and unscheduled visits.

7.10.4 Vital Signs

Vital Signs and changes from baseline, including resting heart rate, diastolic and systolic blood pressure (BP), weight, and height, will be summarized using descriptive statistics at each scheduled visit for vital signs. A listing for vital signs, weight, and height will be provided.

7.10.5 Physical Examination

Abnormalities found in physical examinations will be listed at each scheduled visit for physical examination.

7.10.6 12-lead Electrocardiogram (ECG)

Number and percentage of subjects with normal/abnormal and clinically significant abnormal ECG findings will be summarized at each scheduled visit for 12-lead ECG.

A listing for 12-lead ECG will be provided.

7.10.7 Pregnancy Test

A listing of all pregnancy tests results will be provided.

7.11 Palatability Assessments

In children ≥ 6 years old, patiromer palatability assessments (taste and overall liking) will be summarized using descriptive statistics. A 5-point scale for taste and overall liking includes dislike very much, dislike somewhat, neigher like nor dislike, like somewhat, and like very much.

For children < 6 years old, assessment of the subject's parental acceptance of patiromer will be summarized using descriptive statistics. A 5-point agreement/disagreement scale to a statement of the subject's (< 6 years of age) acceptance of patiromer includes strongly disagree, somewhat disagree, neither agree nor disagree, somewhat agree, and strongly agree.

Appendix A: Schedule of Events (Screening and Pharmacodynamic / Dose Finding Phase)

Study Activity	Phase	Screening			Pharmacodynamic / Dose Finding Phase			ET[b]	MSV[c]
	Scenario	Subject With Standard of Care Potassium	Subject Without Standard of Care Potassium						
	Visit	SV1/D1	SV 1	SV2/D1 (2 to 7 days after SV1)	D3[a] (± 1d)	D7 (± 3d)	D14 (± 3 d)		
Informed Consent		X	X						
I/E Criteria		X		X					
Demographics		X	X						
Medical History		X	X[d]						
Physical Examination		X	X[d]				X	X	
Body Weight		X		X			X	X	
Height		X	X[d]				X	X	
Vital Signs (Resting Heart Rate and Sitting BP)		X	X	X	X	X	X	X	X
12-Lead ECG		X	X[d]		X[m]	X[m]	X[m]	X	X[l]
Potassium		L&C[e]	L	L&C[e]	L&C	L&C	L&C	L&C	L&C
Chemistry[f]		L&C[e]		L&C[e]		C	C	C	
Hematology (CBC)		L&C[e]		L&C[e]			C	C	
Plasma Parathyroid hormone		C[e]		C[e]			C	C	
Serum Fluoride		C[e]		C[e]			C	C	
Urinalysis[g]		C[e]		C[e]			C	C	
Pregnancy Test[h]		L&C[e]		L&C[e]				L&C	
IWRS Entry		X	X	X	X	X	X	X	X
Patiromer Administration[i]		X[e]		X[e]	X[j]	X	X		X
Patiromer Palatability and Parental Assessment[k]		X[e]		X[e]			X		

Appendix A: Schedule of Events (Screening and Pharmacodynamic / Dose Finding Phase) (Cont'd)

Study Activity	Phase	Screening			Pharmacodynamic / Dose Finding Phase			ET [b]	MSV [c]
	Scenario	Subject With Standard of Care Potassium	Subject Without Standard of Care Potassium						
	Visit	SV1/D1	SV 1	SV2/D1 (2 to 7 days after SV1)	D3[a] (± 1d)	D7 (± 3d)	D14 (± 3 d)		
Dosing Diary Dispensation		X		X					
Dosing Diary Review by Investigator/Designee					X	X	X		
Dosing Diary Collection							X		
Drug Accountability & Compliance		X[e]		X[e]	X	X	X	X	X
AE Assessment		X	X	X	X	X	X	X	X
Con Meds Assessment		X	X	X	X	X	X	X	X

AE = Adverse Event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C= Central; D = Day; d = day/days; Laboratory; CBC = Complete Blood Count; Con Meds = concomitant medications; E = exclusion; ET = Early Termination; ECG = Electrocardiogram; eGFR = Estimated Glomerular Filtration Rate; I = inclusion; IWRS = Interactive Web Response System; L= Local Laboratory; SV1= Screening Visit 1; SV2 = Screening Visit 2 (2 to 7 days after SV1); W = Week

[a] Note: At the discretion of the Investigator, the Day 3 Visit is optional for subjects whose last screening K^+ is < 5.5 mEq/L; for subjects whose last screening K^+ is ≥ 5.5 mEq/L, the Day 3 Visit is mandatory (see Section 6.2.2)..

[b] After ET subjects should be encouraged to complete the Follow-up Period Visits (see Section 6.4).

[c] Or any unscheduled visit.

[d] Assessment may be performed either on SV1 or SV2.

[e] Central laboratory measurement or event will not be performed unless subject meets study entry criteria.

[f] For screening, local hematology (CBC including WBC, RBC, hemoglobin, hematocrit, and platelet count) will be performed. Per Investigator's decision, central laboratory assessment of calcium and/or phosphate levels may be tested more frequently for subjects that have one dose of phosphate binder replaced by patiromer.

[g] Not required for anuric subjects; see Section 7.2 for details.

[h] Female subjects of child bearing potential only. For anuric subjects, a serum pregnancy test is required; please Section 7.2 for details.

[i] If patiromer dose requires titration, then initiation of the titrated patiromer dose should occur at the next planned administration (see Section 5.2.1 for details)

[j] Up-titration of patiromer can occur only if the K^+ level is ≥ 5.5 mEq/L and greater than the most recent locally obtained screening potassium value.

[k] Palatability of patiromer will be evaluated in children ≥ 6 years of age when the initial dose is administered at the study site on Day 1 and parental or legal authorized representative response on the subject's (< 6 years of age) acceptance of patiromer will be assessed on Day 14 (see Section 7.6 for further details).

[l] ECG at the Mandatory Safety Visit required only if the local potassium is >6.0 mEq/L at the current or prior visit (see Section 6.5.1)

[m] ECG is only required if the local potassium is > 6.0 mEq/L

Appendix B: Schedule of Events (Long-Term Treatment Phase)

Study Activity	Study Period	Long-Term Treatment Phase								F1 7d ± 3d	F2[a] 14d ± 3d	ET	MSV[b]
	Visit	W3[i] ± 3d	W5 ± 7d	W7 ± 7d	W10[i] ± 7d	W14 ± 7d	W18 ± 7d	W22[i] ± 7d	W26 ± 7d				
Informed Consent													
I/E Criteria													
Demographics													
Medical History													
Physical Examination[k]				X		X			X			X	
Body Weight[k]				X		X			X			X	
Height[k]				X		X			X			X	
Vital Signs (Resting Heart Rate and Sitting BP)		X	X	X	X	X	X	X	X	X		X	X
12-Lead ECG[c]		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]		X	X[j]
Potassium		L & C	L& C	L & C	L& C	L& C	L & C	L& C	L& C	L&C		L& C	L& C
Chemistry[e]				C		C			C	C		C	
Hematology (CBC)				C		C			C			C	
Plasma Parathyroid hormone									C			C	
Serum Fluoride				C		C			C			C	
Urinalysis[f]									C			C	
Pregnancy Test[g]									L& C			L& C	
IWRS Entry		X	X	X	X	X	X	X	X	X	X	X	X

Appendix B: Schedule of Events (Long-Term Treatment Phase) (Cont'd)

Study Activity	Study Period	Long-Term Treatment Phase								F1 7d ± 3d	F2[a] 14d ± 3d	ET	MSV[b]
	Visit	W 3[i] ± 3d	W5 ± 7d	W 7 ± 7d	W 10[i] ± 7d	W14 ± 7d	W 18 ± 7d	W 22[i] ± 7d	W26 ± 7d				
Patiromer Administration[h]		X	X	X	X	X	X	X					X
Drug Accountability & Compliance		X	X	X	X	X	X	X	X			X	X
AE Assessment		X	X	X	X	X	X	X	X	X	X	X	X
Con Meds Assessment		X	X	X	X	X	X	X	X	X	X	X	X

AE = Adverse Event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; d = days; C= Central Laboratory; CBC = Complete Blood Count; Con Meds = concomitant medications; E = exclusion; ET = Early Termination; ECG = Electrocardiogram; eGFR = Estimated Glomerular Filtration Rate; F1 = Follow-up Visit 1 at 7 Days (± 3 days) after the last dose of patiromer; F2 = Follow-up Visit 2 at 14 Days after the last dose of patiromer; I = inclusion; IWRS = Interactive Web Response System L= Local Laboratory; M = months; MSV = Mandatory Safety Visit; W = week

[n] The Phone Call Follow-up may be converted into an Onsite Visit if potassium levels from F1 is of concern by the Investigator and require a re-test. If subjects are requested to return for an onsite visit, the same activities will be performed as those in (F1)

[o] Or any unscheduled visit

[p] When K^+ is > 6.0 mEq/L during the Long-Term Treatment Phase of the study, additional ECG evaluations will be performed.

[q] Per Investigator's decision, central laboratory assessment of calcium and/or phosphate levels may be tested more frequently for subjects that have one dose of phosphate binder replaced by patiromer.

[r] Not required for anuric subjects, see Section 7.2 for details.

[s] Female subjects of child bearing potential only. For anuric subjects, a serum pregnancy test is required; see Section 7.2 for details.

[t] If patiromer dose requires titration, then initiation of the titrated patiromer dose should occur at the next planned administration (see Section 5.2.1 for details).

[u] The last dose of patiromer will be taken the day before the Week 26 Visit.

[v] Week 3, Week 10 and Week 22 visits may be skipped under specific conditions (See Section 3.2.3)

[w] ECG at the Mandatory Safety Visit required only if the local potassium is >6.0 mEq/L at the current or prior visit (see Section 6.5.1)

[x] Study activity may be omitted for Home Care visit (see Section 6.2.5)

[y] ECG is only required if the local potassium is > 6.0 mEq/L

Appendix C: Missing Data Imputation

1 Imputation of Missing/Partially Missing Adverse Event Dates

1.1 Incomplete Start Date

Partially missing AE start/stop dates will be imputed in the ADaM dataset for AEs, according to the rules below. However, listings of AE data will present the date as is, with missing date components left blank.

If the AE end date is complete with no missing year, month, or day, and a partially missing start date imputed by the rules below is after the AE end date, then the imputed start date will be equal to the end date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first doing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed. The corresponding AE will be included as TEAE.

1.2 Incomplete Stop Date

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.