CLINICAL STUDY PROTOCOL

Title:	A Phase 2, 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 (EMERALD)
Investigation Drug:	Patiromer for Oral Suspension
US IND #:	75,615
Protocol Number:	RLY5016-206p
EudraCT:	2016-002785-31
Sponsor:	Relypsa, Inc. 100 Cardinal Way Redwood City, CA 94063 USA. [redacted]
Relypsa Medical Monitor:	[redacted] Executive Medical Director, Clinical Development [redacted]
Protocol Date:	14 March, 2016
Amendment 1 Date:	9 September, 2016
Amendment 2 Date:	10 April 2017
Amendment 3 Date:	27 October 2017
Amendment 4 Date	20 May 2019

[redacted]

PROTOCOL SIGNATURE FORM

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I agree to conduct the study as detailed herein and in compliance with the protocol, International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) and other applicable regulatory requirements.

Principal Investigator Signature **Date**

Principal Investigator Name (print)

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Expert

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This clinical study protocol was subjected to critical review. The information provided is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 2013), and the guidelines on Good Clinical Practices (GCP) applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

[redacted] [redacted]

Date

Executive Medical Director, Clinical Development

Relypsa, Inc.

RLY5016-206P
PROTOCOL AMENDMENT #1
SUMMARY AND RATIONALE FOR CHANGES

The following is a summary of the changes made in this protocol amendment, the sections affected, and the rationale for each change.

No.	Section(s)	Description of Changes	Rationale
1	All	***Global Change:*** • Updated title page, Protocol and Review Signature Form, footers and text to reflect amended protocol version and date • Updated the Table of Contents • Updated the glossary of abbreviations • Update protocol content with punctuation, grammatical, and formatting changes • Updated references	Typographical /Administrative
2	Synopsis	***Added "EMERALD" study name to the study title***	Title update
3	Synopsis 3.2.1 6.1.4	***Revised to allow under certain circumstances, upon approval of the Medical Monitor, an additional screening potassium sample for subjects who meet all eligibility criteria except the last screening potassium value rather than be a screen failure and re-screen***	Revised to provide clarity
4	Synopsis 3.2.1 6.1 6.1.1 6.1.2.2	***Provided additional guidance for eligible subjects who cannot have their last Screening Visit be converted to a Day 1 visit***	Clarification and additional guidance
5	Synopsis 6.2.2 6.2.3 7.5 Appendix A	***ECG will be performed at Day 3 and Day 7 regardless of potassium value***	Simplify study assessments
6	Synopsis 5.3.1	***Added 2 g packet kits***	Additional product presentation for dosing in the 6 to < 12 year age group
7	Synopsis 4.1 7.2	***Included the equation for the Schwartz formula***	Clarification

No.	Section(s)	Description of Changes	Rationale
8	Synopsis Figure 1 Table 1 5.2	***Updated the starting dose levels for the younger age groups from 8.4 g/day to 8 g/day and 4.2 g/day to 4 g/day***	Changed to ensure a single packet size can be used for an age group
9	Synopsis 4.1	***Subject age limitations was updated in the inclusion criteria #2 to ensure that the age does not exceed maximum age specified during the PD / Dose Finding Phase in the age cohort in which they were enrolled***	Clarification to avoid confusion with age cohort assignment
10	Synopsis 3.2.2 8.6.1	***Clarification provided on pausing enrollment during DSMC data review***	Clarification on study process during DSMC review
11	Synopsis 1.4 3.2.2 8.6.1	***Clarification of subject enrollment sequence*** "(or fewer if more than three subjects were initially enrolled)" when describing the nine additional subjects to be enrolled after the first three subjects in the same age group	Clarification for cases where fewer than nine additional subjects may need to be enrolled
12	Synopsis	***Number of study sites updated to 38 from 35 global sites***	Correction
13	Synopsis 5.5	***Broadened recommendation to allow patiromer to replace one of the TID dose for all phosphate binders***	Clarification to include all phosphate binders and not just calcium-based
14	Synopsis 4.1	***Revised inclusion criteria #3 by removing "of any stage as defined by"***	Correction
15	Synopsis 4.2	***Update exclusion criteria #4*** • Added "uncorrected" to pyloric stenosis • Added "[e.g. Hirschsprung disease, chronic intestinal pseudo-obstruction, clinically significant postsurgical abdominal adhesions]" to any other intestinal obstruction	Clarification and providing examples of "other intestinal obstruction"
16	4.3	***Inclusion of potassium-related ECG change as one of the withdrawal criteria***	Administrative
17	4.3	***Updated instructions on subject replacement at Day 14*** • "If a subject withdrew within the 14-Day PD / Dose Finding Phase, the DSMC may be consulted regarding possibility of replacing the withdrawn subject."	Provide further clarification and instructions
18	5.2.1 6.5.1	***Clarification added for anticipated highest dose for subjects in the 2 – < 6 year and 6 – < 12 year age groups***	Provide clarification regarding anticipated highest dose for the two younger age groups

No.	Section(s)	Description of Changes	Rationale
19	Figure 2	***Updated Figure 2***	Typographical corrections and administrative changes for consistency with protocol
20	Table 2 Table 3 Table 4	***Updated Table 2 and included Table 3 and Table 4 with the mixing instructions for possible patiromer doses for each age group***	Provide further patiromer mixing instructions
21	5.3.2	***Updated Patiromer mixing instructions***	Clarified mixing instructions
22	5.3.2	***Guidance provided for subjects with enteral feeding tubes added the following statement:*** "Contact the Relypsa Medical Monitor prior to patiromer administration through an enteral feeding tube."	Additional guidance and clarification
23	5.3.3 6.2.1 6.2.2 6.2.3 6.2.4 Appendix A	***Included description of a Subject Dosing Diary***	Documentation added
24	6.1.1 6.1.2.2	***Clarified which assessments will be performed by the local laboratory for Screening***	Clarification
26	6.2.1 6.2.4 6.2.6 6.4 Appendix A Appendix B Appendix C	***Changed serum PTH to plasma PTH***	Correction
27	6.2.1 Appendix C	***Revised to indicate that both urine and serum samples will be used to evaluate pregnancy***	Update
28	6.2 Appendix A	***Updated visit labels to be more consistent throughout the protocol***	Administrative
29	6.2.5 Appendix B	***Added height to assessments during the Long-Term Treatment Phase***	To ensure the a more complete set of data
30	6.5.1	***Clarified Safety Visit instructions***	Clarification
31	7.7	***Added guidance on fluoride intake***	Added guidance for safety
32	7.8	***Instructions to continue subjects' usual diet during the study***	Added guidance

No.	Section(s)	Description of Changes	Rationale
33	Appendix B	***Corrected Schedule of Events*** • Patiromer administration at the Week 26 Visit was marked in error as the last dose of patiromer is taken the day prior to the Week 26 Visit	Correction
34	Appendix C	***The following clarifications were made to Appendix C:*** • Add total bilirubin to Serum Chemistry panel • Include "(with eGFR by Schwartz formula)" next to Creatinine under Serum Chemistry panel • Under urinalysis, leukocytes changed to "leukocyte esterase" • Deleted "Total CO_2"	Clarification

RLY5016-206P
PROTOCOL AMENDMENT #2
SUMMARY AND RATIONALE FOR CHANGES

The following is a summary of the changes made in this protocol amendment, the sections affected, and the rationale for each change.

No.	Section(s)	Description of Changes	Rationale
1	Title Page, Table of Contents	***Administrative Changes:*** • Updated company logo • Updated title page with study the name "EMERALD" • Updated title page, Protocol and Review Signature Form, footers and text to reflect amended protocol version and date • Updated the Table of Contents	Typographical /Administrative
2	Table of Summary and Rationale of Changes in RLY5016-206p Amendment-1	***Deletion in the Summary of Changes*** • No. 25 in the summary table of changes in protocol RLY5016-206p Amendment-1 was included as an error • Item was never included in protocol.	Typographical correction
3	Synopsis, Section 4.1, Section 7.2 Appendix C	***Added Original Schwartz Formula for Calculating eGFR:*** • Changed from using Bedside to Original or Bedside Schwartz formula to calculate eGFR in Inclusion Criteria #3 • Additional detail on eGFR calculation provided in Section 7.2	Some institutions continue to use older Jaffe methodology for creatinine assay which is only compatible with the Original Schwartz formula for eGFR calculation. This change will allow sites to use the correct GFR estimating formula that corresponds to their intuitional laboratory creatinine assay methodology. This modification applies only to local eGFR measurement.
4	Synopsis Section 3.2.3 Section 6.2.5 Section 6.3.1 Section 7.5 Appendix B	***Clarification of ECG Evaluation at Week 7 and Week 14 Visits and Follow-Up Visit 1***	Clarification

No.	Section(s)	Description of Changes	Rationale
5	Synopsis Section 4.1	***Inclusion Criteria #7*** • Removed "highly"	Clarification
6	Synopsis, Section 4.2 Section 5.5.3, Section 5.6	***Updated Permitted Medications:*** • Removed trimethoprim and cotrimoxazole from Exclusion Criteria #10 and the list of prohibited medications • Allowed trimethoprim for prophylaxis of infections (e.g. urinary tract infection, Pneumocystis carinii pneumonia) • Must be on a stable dose for 14 days prior to Screening and expected to remain on the stable dose during the 14-Day PD / Dose Finding Phase	Many children with CKD may be on low doses of trimethoprim for prophylaxis of UTI or Pneumocystis carinii pneumonia and these low doses are typically administered long-term and are not usually associated with increases in potassium. This update will enhance enrollment and not impact or confound safety or efficacy.
7	Section 3.2.1 Appendix D	***Added Screening Schema*** • Included schema to provide further clarity regarding screening visits	Clarification
8	Section 4.3	***Burden of Risk Monitoring:*** • Provided clarification that the investigator should monitor the burden and risk of participation on an ongoing basis. • Participation in the study should only be continued if the investigator determines there is no more than a minimal increase over the burden and risk that are described in the protocol or associated with routine clinical examinations, clinical care and treatment of patients with chronic kidney disease and hyperkalemia.	Clarification
9	Section 5.3	***Additional Instructions on Patiromer Use:*** • Updated with the following statement: "Consult the Pharmacy Manual for details on patiromer administration through an enteral feeding tube."	To allow patiromer to be administered through an enteral feeding tube in subjects with gastrostomy or NG tubes.

No.	Section(s)	Description of Changes	Rationale
10	Figure 2 Section 5.5.1.1 Section 6.5.1	***Clarification of Unscheduled Safety Visits*** • Revised text to clarify that an unscheduled visit may occur at any phase of the study, including during the Follow-Up Phase prior to the scheduled Day 7 visit at the investigator's discretion • Rationale for possible unscheduled visit prior to Day 7 of Follow-Up Phase is included • Figure 2 footnote was also updated	Clarification
11	Section 5.5.2	***Additional Instructions Provided for Anti-rejection Medication*** • Additional instructions provided in the event that the dose of anti-rejection medication requires adjustment during the 14-Day PD/Dose Finding Phase	Additional guidance and clarification
12	Section 5.5.4	***Additional Guidance on Peritoneal Dialysis Prescription:*** • Added "The prescription for peritoneal dialysis should not be modified during the 14-Day PD / Dose Finding Phase of the study"	For safety reasons and to minimize effects that may confound the efficacy parameters
13	Section 6.1.4	***Correction of Section Reference*** • Section 6.1.4 should be referenced not 6.1.3	Typographical correction
14	Section 6.2.1	***Correction of Typographical Error in Study Assessments*** • Removal of "other" when referencing central laboratory test to avoid confusion	Typographical correction and clarification
15	Section 7.6	***Clarification of Palatability Assessment at Day 1*** • Patiromer should be mixed in water for palatability assessment	Clarification
16.	Section 8.3.2	***Clarification of the Suspected Unexpected Serious Adverse Reaction (SUSAR) Reporting Obligations***	Clarification
17	Section 8.6.2	***Updated Stopping Criteria*** • Provided further guidance regarding stopping rules in the case of a SUSAR	Revision

RLY5016-206P
PROTOCOL AMENDMENT #3
SUMMARY AND RATIONALE FOR CHANGES

The following is a summary of the changes made in this protocol amendment, the sections affected, and the rationale for each change.

No.	Section(s)	Description of Changes	Rationale
1	Title Page, Table of Contents, Abbreviations Synopsis, Section 1, Section 1.2 Section 4.2, Section 5.5.1.2, Section 15	***Administrative Changes:*** • Updated title page, Protocol and Review Signature Form, footers and text to reflect amended protocol version and date • Updated the title page with new company logo • Updated the Table of Contents • Added EU approval of Veltassa and SmPC reference • Heart failure is written out rather than abbreviated as "HF"	Typographical /Administrative
2	Synopsis, Section 3.2.1, Section 6.1 Section 6.1.3	***Rescreening of Subjects:*** • Retest of screening serum potassium was removed • Subjects who screen fail may be rescreened once after approval from the Medical Monitor	To simplify subject rescreening and the study operationally
3	Synopsis, Section 3.2.2, Section 5.2.1, Section 5.3.3, Section 6.2.2, Section 7.5, Appendix A	***Day 3 Visit:*** • Day 3 Visit may be optional (at the investigator's discretion) for enrolled subjects whose last screening K^+ is < 5.5 mEq/L • Day 3 Visit is mandatory for enrolled subjects whose last screening K^+ is ≥ 5.5 mEq/L	To reduce the burden of the number of visits for qualifying subjects while maintaining subject safety
4	Synopsis, Section 5.3.2, Section 5.3.3,	***Dosing Patiromer without Food:*** • Subjects may take patiromer with food or without food	Simplified dosing instructions based on findings from a recent Patiromer food effect study which showed patiromer demonstrated the same efficacy and safety when taken either with or without food

No.	Section(s)	Description of Changes	Rationale
5	Synopsis Section 4.2, Section 5.6	***Prohibiting Use of or Sodium Zirconium Cyclosilicate***	In anticipation of marketing of sodium zirconium cyclosilicate, it was added to the list of prohibited medications as use may confound the study findings
6	Synopsis, Section 4.1 Section 7.2	***Clarification of Schwartz Formula Use:*** • Removed "Original or Bedside" and added Section 7.2 reference for the Schwartz formula in Inclusion Criteria #3 • For local labs that use the Jaffe assay to calculate eGFR, if the assay is isotope dilution mass spectrometry (IDMS) traceable, then the bedside Schwartz formula should be used	Clarified when to use the Original or Bedside versions of the Schwartz formula in Section 7.2 of the protocol, and cross referenced other mentions of the Schwartz Formula in the protocol Central laboratory is using an IDMS traceable Jaffe assay; therefore, the clarification is added to ensure consistency across study sites
7	Synopsis	***Alignment of Efficacy Analysis, Safety Outcomes and Analysis, and Additional Analysis Described in Synopsis with Section 9: Data Analysis / Statistical Methods***	Correcting misalignment between synopsis and Section 9
8	Synopsis, Section 5.5.4	***Use of Fludrocortisone:*** • Fludrocortisone dose must be stable for at least 28 days prior to screening • During the 14-Day PD/Dose Finding Phase, dose adjustments to fludrocortisone should not be made • During the Long-Term Treatment Phase adjustments to fludrocortisone are permitted for safety reasons	Fludrocortisone was not previously described in the protocol; however, this medication decreases serum potassium and could interfere with evaluation of patiromer effect, chronic use with stable doses should have minimal effect on serum potassium and thus can be allowed in these situations
98	Section 6.1	***Clarification of Subject Identifier*** • Updated "unique subject identification number" with "unique study subject identification number"	Clarification

No.	Section(s)	Description of Changes	Rationale
10	Section 6.1.2.2, Section 6.2.6, Section 6.4, Section 7.2, Appendix A Appendix B	***Urine Pregnancy Test in the Case of Anuric Subjects:*** • Anuric subjects may have a serum pregnancy test instead of urine pregnancy test at Day 1	To allow anuric subjects into the study
11	Section 6.2.1, Section 6.2.4, Section 6.2.6, Section 6.4, Section 7.2, Appendix A, Appendix B	***Urinalysis in the Case of Anuric Subjects*** • No urinalysis will be performed on these subjects	To allow anuric subjects into the study
12	Section 7.7	***Further Clarification of Items to be Carefully Supervised by Guardian Due to Fluoride Content:*** • Added dental rinse	Clarification
13	Section 8.5	***Added Reference to "SMC Plan"***	Erroneously omitted
14	Section 8.6.3	***Clarification of Frequency of DSMC Meetings*** • Added information regarding DSMC meetings after the dose expansion group of 9 subjects complete their 14-day PD / Dose Finding Phase • Added information that if a subject withdraws from the study within the 14-Day PD / Dose Find Phase, the SMC determines if sufficient information is provided for DSMC review, and the DSMC meeting may be delayed if insufficient information is provided	Clarification / erroneously omitted

RLY5016-206P
PROTOCOL AMENDMENT #4
SUMMARY AND RATIONALE FOR CHANGES

The following is a summary of the changes made in this protocol amendment, the sections affected, and the rationale for each change.

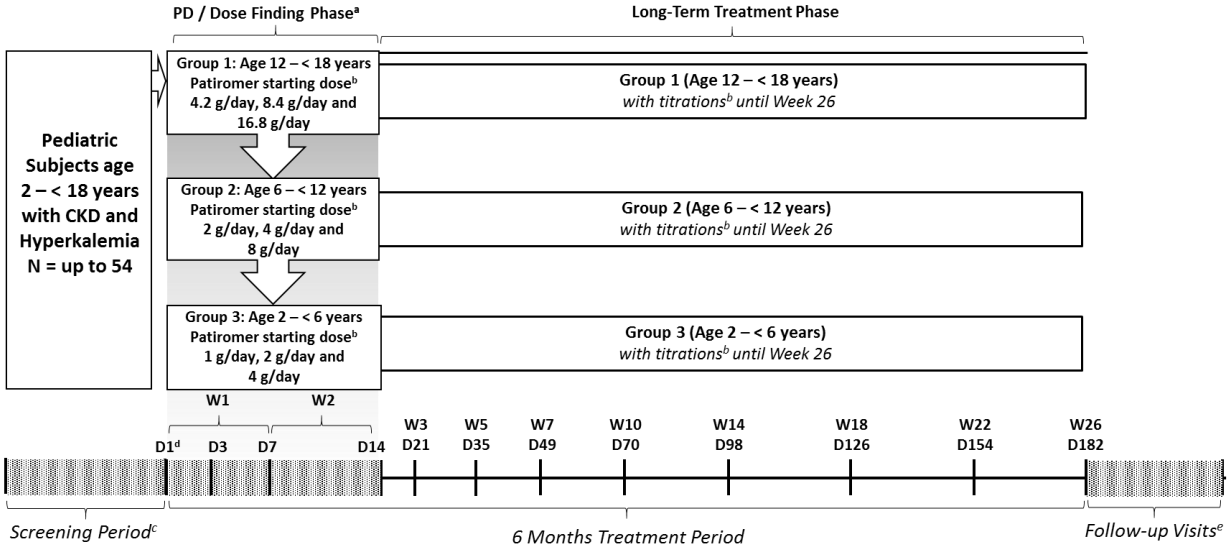
No.	Section(s)	Description of Changes	Rationale
1	Synopsis Section 4.1 Section 7.2	***Updated Inclusion Criteria #3:*** • Raised eGFR eligibility from < 60 mL/min/1.73m^2 to < 90 mL/min/1.73m^2 • Removed peritoneal dialysis.	To allow hyperkalemic subjects with earlier stages of CKD (CKD2) to enroll Updated per 25Sep18 DSMC guidelines for management of subjects transitioning to dialysis during the study
2	Synopsis Section 3.2.2 Section 3.2.3 Section 6.2.2 Section 6.2.3 Section 6.2.4 Section 6.2.5 Section 6.3.1 Section 6.5.1 Section 7.5 Appendix A Appendix B	***Updated Requirements for ECG Evaluation:*** • 12-lead ECG is only required at baseline and Week 26 or if the local K+ is > 6.0 mEq/L at that visit • A 12-lead ECG is required at an MSV if the most recent local potassium is > 6.0 mEq/L	Reduce burden on subjects during study visits while maintaining safety; clarification for use of only local potassium level in determining need for ECG
3	Synopsis Section 4.2	***Updated Exclusion Criteria #3:*** • Removed restriction on planned need for hemodialysis during the study • Added exclusion of subjects on maintenance peritoneal dialysis	Updated per 25Sep18 DSMC guidelines for management of subjects transitioning to dialysis during the study
4	Section 4.3 Section 4.4	***Additional Guidance on Hemodialysis and Peritoneal Dialysis:*** • Added transition to dialysis during study and reason for study withdrawal • Added DSMC guidance for subjects transitioning to maintenance hemodialysis and peritoneal dialysis • Patients who are anticipated to require dialysis shortly after enrollment (within 6-8 weeks of Day 1) may not be suitable for enrollment due to unstable medical status and fluctuating potassium levels.	Updated per 25Sep18 DSMC guidelines for management of subjects transitioning to dialysis during the study; improves management of subjects with progression of CKD

		Removed Section 5.5.5	
5	Section 5.2.1 Section 6.5.1	***Updated Timing Requirement for an MSV*** • Extended the requirement for Mandatory Safety Visits from within 72 hours to within 7 days	To simplify the study operationally and reduce burden on subjects while maintaining safety
6	Synopsis Section 3.2.3 Section 6.2.5 Appendix B	***Updated Long-Term Treatment Phase Schedule of Events*** • Week 3, Week 10 and Week 22 may be omitted under certain circumstances; refer to section 3.2.3 for details • Addition of home care visits during the long-term treatment phase. Up to 2 non-sequential study visits may be conducted remotely using the Sponsor approved Home Care vendor at certain approved investigational sites in certain countries • Certain study procedures may be omitted at Home Care Visits.	To reduce the burden of the number of visits for qualifying subjects while maintaining subject safety

STUDY SYNOPSIS

Title:	A Phase 2, 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 (EMERALD)
Protocol Number:	RLY5016-206p
Phase:	Phase 2
Description of Agent or Intervention:	Patiromer for Oral Suspension (patiromer) is a polymeric drug designed to bind and remove potassium from the gastrointestinal tract. Patiromer (Veltassa®) is approved by the Food and Drug Administration (FDA) and the EMA (European Medicines Agency) for the treatment of hyperkalemia in adult patients.
Study Objectives	
Study Objectives:	Primary: 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. Secondary: To assess the safety and tolerability of patiromer in children 2 – < 18 years of age with CKD and hyperkalemia.
Study Outcomes	
Primary Efficacy:	Change in serum potassium levels from baseline to Day 14.
Secondary Efficacy:	• Proportion of subjects with serum potassium levels in the range of 3.8 – 5.0 mEq/L at Day 14 (Initial Pharmacodynamic [PD] / Dose Finding Phase) • Proportion of subjects with serum potassium levels in the range of 3.8 – 5.0 mEq/L by visit through Month 6 (Long-Term Treatment Phase)
Safety:	Safety analyses will include: • Incidence and severity of adverse events (AEs) • Changes from baseline in clinical laboratory values (hematology and serum chemistry including serum magnesium, serum calcium and serum fluoride) • Changes from baseline in vital signs and electrocardiogram (ECG)
Study Design	
Description:	Up to 54 subjects, 2 – < 18 years of age with CKD (estimated glomerular filtration rate [eGFR] < 90 mL/min/1.73 m^2 calculated using the Schwartz formula (see Section 7.2) and hyperkalemia (two potassium measurements of 5.1 to < 6.5 mEq/L performed on separate days) 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 Study Schema). The overall design of the study is presented schematically below.

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.

Screening (up to 7 Days):

Subject's eligibility will be assessed during a Screening Period with up to two visits (Screening Visit 1, Screening Visit 2). Eligibility for this study requires the presence of hyperkalemia assessed by two blood or serum potassium measurements performed on separate days; qualifying potassium values are 5.1 to < 6.5 mEq/L. A standard of care potassium value measured within 42 days to 2 days prior to Screening may be used for one of the potassium values to assess eligibility. The following scenarios are allowed for obtaining the two qualifying potassium values (5.1 to < 6.5 mEq/L):

- For subjects **with a recent standard of care potassium measurement**, the two qualifying potassium values will be the most recent standard of care potassium measurement obtained from 42 days to 2 days prior to Screening Visit 1 and the local potassium measurement at Screening Visit 1.
- For subjects **without a recent standard of care potassium** measurement within 42 days to 2 days prior to Screening Visit 1, the first qualifying potassium value will be obtained at Screening Visit 1 and the second at Screening Visit 2, occurring 2 to 7 days after Screening Visit 1.

For subjects who meet all eligibility criteria at either Screening Visit 1 or Screening Visit 2, that visit should be converted to the Day 1 Visit (Baseline). In cases where this is not possible, eligible subjects must return the next day to complete the Day 1 Visit.

Subjects who screen fail may be rescreened once upon approval of the Medical Monitor, see Section 6.1.3).

	14-Day PD / Dose Finding Phase: Study visits will occur at Day 1, Day 3, Day 7 and Day 14 when potassium concentrations will be measured locally and by the central laboratory (see Schedule of Events, Appendix 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). Additional laboratory assays (Appendix C) will be performed at specified visits according to the Schedule of Events Appendix A). 12-lead ECGs will be performed at Day 3, 7, and 14 Visits if the local K+ is >6.0 mEq/L at that visit. A full list of central laboratory assays is provided in Appendix C. Eligible subjects will be categorized into three different age cohorts (12 – < 18 years, 6 – < 12 years, and 2 – < 6 years). Enrollment will start with the oldest age cohort first; this is to ensure safety of younger age subjects who might be the most vulnerable to potential adverse events associated with patiromer. Initiation of enrollment of subjects in the younger age cohorts will depend on Data and Safety Monitoring Committee (DSMC) review (See DSMC Review section below for further details). Up to three starting dose levels will be evaluated in each age group. The initial dose evaluated will be the lowest of the planned starting dose levels for each age group. The planned starting dose levels are: • Age 12 – < 18 years: 4.2 g/day, 8.4 g/day, 16.8 g/day • Age 6 – < 12 years: 2 g/day, 4 g/day and 8 g/day • Age 2 – < 6 years: 1 g/day, 2 g/day and 4 g/day Note: the starting doses may require modification based upon the DSMC recommendation after their review of the safety and PD data (see DSMC Review section below for further details). Patiromer dose titration is allowed per a protocol-specified algorithm (see Section 5.2.1). The titrated increment or decrement is planned to be the lowest starting dose for each age group. Long-Term Treatment Phase: The Long-Term Treatment Phase consists of eight visits over a period of 5.5 months. Study visits occur at Week 3, Week 5, Week 7, Week 10, Week 14, Week 18, Week 22 and Week 26. At each study visit potassium levels, measured locally and by central laboratory, will be obtained. ECG evaluations will be performed as soon as possible whenever the K^+ level is > 6.0 mEq/L; at the Week 26 Visit, an ECG will be performed regardless of potassium level. Additional laboratory assays and assessments will be performed according to the Schedule of Events (see Appendix B). A full list of central laboratory assays is provided in Appendix C. Study visits at Week 3, Week 10 and Week 22 may be omitted if specific criteria are met including achieving potassium levels in the target range (3.8-5.0 mEq/L) at the prior visit (see Section 3.2.3). During the Long-Term Treatment Phase, up to 2 non-sequential study visits may be conducted remotely using a Sponsor approved Home Care vendor at certain investigational sites in certain countries; Week 26 may not be a Home Care visit. Dose adjustments in the Long-Term Treatment Phase may be made at each study visit starting with the Week 2 (Day 14) Visit according to the titration algorithm (see Section 5.2.1). The titrated increment or decrement is planned to be the lowest starting dose for each age group. Follow-up Period: After the patiromer Treatment Periods, subjects will enter the Follow-up Period, which will consist of one Visit at 7 days (Follow-up Visit 1) and one phone call at 14 days after

	stopping patiromer treatment (Follow-up Visit 2). All subjects who withdraw early from treatment will enter the Follow-up Period.
DSMC Review / Starting Dose Level Assessment:	The DSMC will determine a recommended starting dose for each age group. After three subjects at a given starting dose level provide data from the 14-Day PD / Dose Finding Phase, the DSMC will evaluate safety and PD data, including achievement of serum potassium within the target range (serum K^+ 3.8 – 5.0 mEq/L) and the PD response pattern as well as the number of subjects requiring dose titration. Based on this review, the DSMC will provide a recommendation to evaluate another starting dose in the age group or to evaluate the current starting dose in additional subjects in the age group. Details regarding DSMC review criteria will be described in a charter and are summarized in the DSMC section of the protocol (Section 8.6). The initial number of subjects for each starting dose level will be three, and up to three starting doses per age group can be evaluated. Subject screening will pause periodically throughout the study to allow for preparation of data and DSMC review and provision of recommendations. Any subjects who are in the Screening Period when the pause is announced may be enrolled provided they meet all eligibility criteria. When the Study Management Committee (SMC; see Section 8.5) and DSMC agree upon the recommended patiromer starting dose for a particular age group based upon safety and PD data review, nine additional subjects (or fewer if more than three subjects were initially enrolled) will be added in that age group to receive the recommended patiromer starting dose. Subjects will not be enrolled into higher starting dose levels once the recommended patiromer starting dose is determined for a particular age group. This will yield a total of 12 subjects per age group at the recommended starting dose and a maximum of 18 subjects per age group. Based on findings from the 12 – < 18 years of age cohort, the DSMC will provide a recommendation to initiate dosing in a younger age group, and provide further guidance regarding the starting doses and titration increments for the younger age groups. In addition, the DSMC will review safety and PD data on an ongoing basis during the Long-Term Treatment Phase for all age groups.
Study Duration:	Individual subject participation up to 6.5 months consisting of: Screening / Day 1 followed by 14-day PD / Dose Finding Phase, 5.5-month Long Term Treatment Phase, and a 2-week Follow-up Period consisting of one Follow-up Visit and one Follow-up Phone Call.
Study Sites:	Up to 38 sites globally.
Study Population:	Up to 54 subjects aged 2 to < 18 years old.
Study Treatments	
Dose and Route of Administration:	Investigational Product: Patiromer Patiromer will be given once daily (QD). The starting doses of patiromer in each age cohort were selected based on the median weights for boys and girls within each of the three age categories using standard growth data (CDC 2010). The initial weight-based doses selected were guided by the starting dose in adults (8.4 g/day patiromer), a higher commonly used dose in adults (16.8 g/day) and a dose below the adult efficacy range (4.2 g/day patiromer) in the event children have a different response profile than in adults. Patiromer will be provided open-label to subjects as a powder for oral suspension in packets with appropriate labeling. The individual packets will be assembled as a kit for dispensing the adequate amount of patiromer for each subject. Each packet inside an individual kit will contain either 4.2 g, 2.0 g, or 1.0 g patiromer. Subjects and their parent or legally authorized representative will be instructed to mix patiromer with water, apple juice or cranberry juice. Subjects and their legally authorized representative will be instructed that patiromer can be taken with or without food. Patiromer should be taken 3 hours before or 3 hours after administration of other concomitant medications. At the discretion of the Investigator, the following drugs may be coadministered with patiromer: allopurinol, amlodipine, amoxicillin, apixaban, aspirin, atorvastatin, cephalexin, cinacalcet, clopidogrel, digoxin, furosemide, glipizide, lisinopril,

	lithium, metoprolol, phenytoin, rivaroxaban, spironolactone, trimethoprim, valsartan, verapamil, and warfarin. For subjects taking phosphate binders three times daily (TID) and for whom in the opinion of the investigator one dose per day of the phosphate binder can be replaced by patiromer, patiromer may be dosed with the same meal each day and the phosphate binder dosed with two other meals each day.
Eligibility Criteria	
	Inclusion Criteria: Subjects must meet ALL the following criteria: 1. Written assent (when applicable) and written informed consent by a legally authorized representative provided prior to participation in the study 2. Age 2 – < 18 years old (subject's age should not exceed that of the age cohort into which s/he is enrolled for at least the entire 14 days of the PD / Dose Finding Phase) 3. Pediatric subjects with CKD and eGFR < 90 mL/min/1.73m^2 calculated using the Schwartz formula as described in Section 7.2, including renal transplant subjects, based on local creatinine measurement at Screening 4. Two blood or serum potassium measurements of 5.1 to < 6.5 mEq/L performed on separate days (see Section 6.1) 5. In the opinion of the Investigator, the subject is expected to require treatment for hyperkalemia for at least 6 months 6. If taking any renin-angiotensin aldosterone system inhibitors (RAASi), beta blockers, fludrocortisone or diuretic medications, must be on a stable dose for at least 28 days prior to Screening 7. Females of child-bearing potential must be non-lactating, must have a negative pregnancy test at Screening, and must have used an effective form of contraception (e.g. abstinence, hormonal, chemical, physical barrier, etc.) for at least 1 month before patiromer administration. Subjects of child-bearing potential must agree to continue using contraception throughout the study and for 1 month after the last dose of patiromer **Exclusion Criteria:** Subjects must NOT meet ANY of the following exclusion criteria: 1. Subjects with pseudohyperkalemia due to hemolysis or to abnormally high numbers of platelets (> 500,000/mm^3), leukocytes (> 70,000/mm^3), or erythrocytes (hematocrit > 55%) at Screening based on results obtained locally 2. Any subject with evidence of potential potassium-related ECG changes (i.e., changes consistent with hyper- or hypokalemia) at Screening 3. Any of the following renal conditions: maintenance hemodialysis or peritoneal dialysis, renal artery stenosis, and acute kidney injury (defined by 2012 Kidney Disease Improving Global Outcomes [KDIGO], 2012) or a history of acute renal insufficiency in the past 3 months 4. A history of or current diagnosis of a severe gastrointestinal diagnosis or surgery that could affect gastrointestinal transit of the drug (e.g. a severe swallowing disorder, uncorrected pyloric stenosis, intussusception, any other intestinal obstruction [e.g., Hirschsprung disease, chronic intestinal pseudo-obstruction, clinically significant postsurgical abdominal adhesions] or any gut-shortening surgical procedure prior to Screening) 5. A history of or current diagnosis of a condition that in the opinion of the investigator increases the risk of aspiration of patiromer if it will be given orally

	6. Liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST) > three times upper limit of normal at Screening, based on the local laboratory ALT and AST 7. Active cancer, currently on cancer treatment or history of cancer in the past 2 years (except for non-melanoma skin cancer) 8. Heart or liver transplant recipient, or anticipated need for transplant during the study Treatment Period, including a scheduled kidney transplant recipient (note: patients currently on a kidney transplant wait list are not excluded unless there is an identified donor) 9. Chronic alcohol abuse or substance use disorder within 1 year of Screening 10. Subjects currently being treated with or having taken any one of the following medications (includes resins) in the 7 days prior to Screening: sodium or calcium polystyrene sulfonate, sodium zirconium cyclosilicate, and drospirenone 11. Use of the following medications if doses have not been stable for at least 14 days prior to Screening or if doses are anticipated to change during the 14-day PD / Dose Finding Phase: - digoxin; - bronchodilators; - theophylline; - heparins (including low molecular heparins); - canagliflozin; - tacrolimus; - mycophenolate mofetil; - cyclosporine - trimethoprim or cotrimoxazole 12. Use of any investigational product for an unapproved indication within 30 days prior to Screening or within 5 half-lives, whichever is longer 13. Known hypersensitivity to patiromer or its components 14. In the opinion of the Investigator, inability to comply with the protocol 15. In the opinion of the Investigator, any medical condition, uncontrolled systemic disease, or serious intercurrent illness that would significantly decrease study compliance or jeopardize the safety of the subject or potentially affect the quality of the data such as: hyperkalemia at Screening that requires emergency intervention; cardiovascular event or intervention within 3 months prior to Screening; a hemodynamically unstable arrhythmia; hospitalization for heart failure within the past 3 months; poorly controlled blood pressure (BP); poorly controlled diabetes mellitus or frequent need for adjustment in insulin prescription or recent hospitalization for treatment of hyper or hypoglycemia
Statistical Methods	
Determination of Sample Size:	This study will enroll up to 54 subjects. For children ages 2 to < 18 years, the total sample size could be as low as 36 (three initially treated subjects plus an additional nine if the first dose is chosen as safe and effective for each of the three different age cohorts) or up to 54 if all three dose levels are studied for each age group.

Randomization:	This is an open-label, non-randomized study.
Efficacy Analysis:	Change in serum potassium will be summarized by starting dose and age group using descriptive statistics. The proportion (number and percentage of subjects) with serum K^+ levels in the range of 3.8 – 5.0 mEq/L will be summarized by visit; the 95% confidence interval will be presented.
Safety Analysis	Safety variables will consist of all AEs, severe adverse events (SAEs), clinical laboratory test results (including serum potassium, calcium, magnesium, phosphate, and fluoride), vital signs and ECG, and reasons for dosing interruption or discontinuation.
Additional Analysis	For children ≥ 6 years old, evaluation of patiromer palatability at first dose (Day 1) will be performed using a visual analogue scale score; for children < 6 years old parental or authorized legal representative response of the subject's acceptance of patiromer will be assessed on Day 14. These assessments will be summarized using descriptive statistics.

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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
Con Meds	Concomitant Medications
CKD	Chronic Kidney Disease
CRF	Case Report Form
C_{max}	Maximum Concentration
D	Day
DAIDS	Division of AIDS
DSMC	Data and Safety Monitoring Committee
E	Exclusion
EC	Ethics Committee
ECG	Electrocardiograms
EMA	European Medicines Agency
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
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
SmPC	Summary of Product Characteristics
TID	Three Times Daily
US	United States
W	Week
WBC	White Blood Cell Count

1 INTRODUCTION

Patiromer for Oral Suspension (patiromer) is a nonabsorbed, cation-exchange polymer that has been developed for the treatment of hyperkalemia. Patiromer binds potassium (K^+) predominantly in the lumen of the colon and increases fecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels. The drug substance consists of the polymer anion (the active moiety, patiromer) and a calcium-sorbitol counterion complex.

Patiromer (Veltassa®) is approved by the FDA and EMA for the treatment of hyperkalemia in adults (Veltassa PI, 2016, Veltassa SmPC, 2017).

1.1 Background

Serum potassium concentration is carefully regulated within a normal range of 3.8 – 5.0 mEq/L in adults (Rodriguez-Soriano, 1995) and approximately 90% of potassium is excreted by the kidney and 10% is excreted by the colon (Schaefer, 2005). Hyperkalemia is commonly defined as a serum potassium level above the upper limit of normal (i.e., > 5.0 mEq/L in both adults and pediatric patients). The physiologic effects of hyperkalemia can cause muscle weakness, paralysis and life threatening effects on cardiac conduction (e.g., QRS widening), arrhythmias, such as ventricular fibrillation, and sudden death (Ahmed, 2001). The deleterious effects of elevated potassium have been observed at levels as low as 5.0 mEq/L (Jain, 2012, Miao, 2011).

As in adults, children most at risk for hyperkalemia are those with CKD. In patients with CKD, the primary cause of hyperkalemia is a decrease in renal elimination of potassium, and the risk of hyperkalemia increases as renal function deteriorates (Wong, 2006). Furthermore, the use of drugs that block the renin angiotensin aldosterone system (RAAS) can increase the risk and severity of hyperkalemia in patients with underlying CKD. Given that this class of drugs has been proven to slow progression of renal disease among children with progressive CKD due to primary glomerulopathies or renal hypoplasia-dysplasia (The ESCAPE Trial Group, 2009), the management and treatment of hyperkalemia is critically important to enable the use of these agents (Wong, 2006).

Approximately 8 – 36% of adults with CKD develop hyperkalemia (Einhorn, 2009, Tzamaloukas, 1987) as defined by a serum potassium concentration > 5.0 mEq/L, which is often treated or prevented with diet, dose modifications of contributing medications, and/or dialysis (Lu, 2009). In children with CKD, the prevalence estimate of hyperkalemia has been reported in 366 patients (mean age 9.9 ± 5.1 years) at a single large pediatric nephrology center in Canada (Wong, 2006). A patient was considered to demonstrate hyperkalemia if any of the following three criteria were met: 1) any treatment with potassium binders; 2) potassium dietary restrictions; or 3) the most recent serum potassium was > 6.0 mmol/L. While the high cutoff for serum potassium as an inclusion criterion in this study may lead to an underestimation of the prevalence of hyperkalemia in CKD pediatric patients, the general tendency of increasing frequency of hyperkalemia with increasing stage of CKD is similar to the observed pattern in adults: the prevalence of hyperkalemia in children with CKD ranged from 0.9% in CKD stage 2 (GFR range 60 – 90 mL/min/1.73m^2) to 5.3% in CKD stage 3 (GFR range 30 - < 60 mL/min/1.73m^2) and 18.2 % in CKD stage 4 and 5 combined (GFR range 15 – < 30 mL/min/1.73m^2 and < 15 mL/min/1.73m^2).

An analysis of the serum potassium data from the ongoing Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study in Europe provides additional estimates of the frequency of hyperkalemia in the pediatric CKD population. The 4C study is a longitudinal observational study following approximately 700 children with CKD ages 6 to 17 years at the time of enrollment, and is evaluating the prevalence, clinical symptoms and progression of cardiovascular and kidney disease (Querfeld, 2010). Mild hyperkalemia defined as serum potassium of 4.8 - 5.4 mEq/L, occurred in 11.6 % of the samples analyzed in children with CKD stage 2 and increased up to 28.6 % in children with CKD stage 4 and 33.8 % in children on hemodialysis. Moderate hyperkalemia (5.5 – 5.9 mEq/L) and severe hyperkalemia (≥ 6 mEq/L), although both occurring at a lower rate, showed a similar pattern in increasing frequency with worsening kidney disease.

Hyperkalemia can occur acutely and also can be a recurring condition in patients with the above chronic conditions and drug treatments; however, the utility of current options for the management of hyperkalemia (e.g., dietary potassium restriction, diuretics, sodium bicarbonate, sodium and calcium polystyrene sulfonate) are limited and not all of them have been well studied for treatment of hyperkalemia. Some treatments for hyperkalemia such as insulin and bicarbonate, shift potassium intracellularly, but do not reduce total body potassium.

Given the limitations with current therapies and the need for a well-tolerated potassium binder to be used in both acute and chronic clinical settings, patiromer was developed as an alternative therapy for patients with hyperkalemia.

1.2 Effects in Humans

The clinical development program for patiromer to date includes eight completed studies: three Phase 1 studies, four Phase 2 studies and one two-part Phase 3 study (RLY5016-301). A total of 791 subjects participated in these eight clinical studies, including patients with hyperkalemia, CKD, heart failure, diabetes mellitus, hypertension and/or patients on hemodialysis, and healthy volunteer subjects. The 734 subjects received at least one dose of patiromer and the duration of dosing ranged from a single dose to up to 1 year.

The pivotal two-part Phase 3 study (RLY5016-301) evaluated the treatment of hyperkalemia in subjects with CKD at two starting doses, 4.2 g patiromer BID or 8.4 g patiromer BID (subjects with screening serum K^+ of > 5.0 to < 5.5 mEq/L were assigned the lower starting dose and subjects with screening serum K^+ of 5.5 to < 6.5 mEq/L were assigned the higher starting dose) (Weir, 2015). The study consisted of two parts (Part A, a 4-week treatment phase, and Part B, an 8-week, placebo-controlled, randomized withdrawal phase). In Part A, the mean (SE) change in serum potassium from baseline (mean [SD] 5.58 [0.51] mEq/L) to Week 4 was -1.01 (0.031) mEq/L (95% CI: [-1.07, -0.95]); this mean reduction in serum potassium was statistically and clinically significant. The proportion of subjects with a serum potassium level in the Part A target range of target range of 3.8 to < 5.1 mEq/L at Week 4 was 76% overall. The proportion of subjects in the target range was similar in both starting dose groups, which had been assigned according to severity of starting serum potassium level. Randomized withdrawal of the drug in the second part (Part B) confirmed the efficacy observed in Part A and provided evidence of the benefit of continued treatment with patiromer once serum potassium is controlled.

Two Phase 1 studies in healthy volunteers (RLY5016-101 and RLY5016-102) demonstrated that doses of up to 50.4 g/day patiromer were pharmacologically active (resulting in increased fecal potassium excretion in a dose-dependent manner) and well-tolerated, and that 25.2 g/day patiromer administered either QD, BID, or TID had similar pharmacological activity and tolerability. The safety, tolerability, and pharmacologic activity of QD dosing of patiromer were assessed in Study RLY5016-102. This open-label, multiple-dose crossover Phase 1 study evaluated the pharmacology, safety and tolerability of three dosing regimens of patiromer in 12 healthy subjects. Patiromer was administered orally as an aqueous suspension of 8.4 g patiromer TID for 6 days, 12.6 g patiromer BID for 6 days and 25.2 g patiromer QD for 6 days in a randomly assigned order based on one of six dosing sequences. Administration of 25.2 g/day patiromer led to a mean increase in fecal potassium excretion of approximately 1400 mg/day, with a corresponding similar decrease in urinary potassium excretion. No statistically significant difference was observed among the TID/BID/QD treatment groups with respect to the mean daily fecal or urinary potassium excretion. This was true for the overall comparison among the three treatment groups, as well as for the pairwise comparisons.

The onset of action Phase 1 study RLY5016-103 in subjects with hyperkalemia provided additional information supporting QD dosing of patiromer (Bushinsky, 2015). This was an open-label, single arm study that evaluated the time to onset of the potassium-lowering action of patiromer. Twenty-five (25) subjects with CKD (baseline mean eGFR of 34.8 mL/min/1.73m^2) who had a serum potassium at Screening of 5.5 to < 6.2 mEq/L and who were not on dialysis were entered into a 3-day in-patient run-in period during which they began receiving a potassium- and sodium-controlled diet, followed by a 48-hour treatment period (fixed dose of 8.4 grams patiromer BID for a total of 4 doses, administered at Hours 0, 10, 24 and 34) during which serum potassium was assessed repeatedly. From a mean baseline serum potassium of 5.93 mEq/L, statistically significant reductions were observed at 7 hours after the first dose (0.21 mEq/L) and throughout the 48-hour treatment period ($p \leq 0.001$). After the last dose of patiromer at Hour 34, mean serum potassium values continued to decline, reaching a mean (standard deviation [SD]) maximal reduction of 0.83 (0.454) mEq/L at 7 hours after the last dose (Hour 41). By Hour 58 (i.e., 24 hours following the last dose), the mean serum potassium had returned to a level similar to that at the time of the last dose (mean [SD] serum potassium at Hour 34: 5.28 [0.373] mEq/L; at Hour 41: 5.11 [0.391] mEq/L; at Hour 58: 5.27 [0.548] mEq/L).

A comprehensive assessment of safety of patiromer for the treatment of hyperkalemia was conducted. A total number of 734 adults were exposed to at least one dose of patiromer and a pooled safety analysis was conducted in 666 subjects receiving patiromer (including 219 exposed for at least 6 months and 149 exposed for at least one year) and 49 subjects receiving placebo for up to 28 days. Data from the overall safety population demonstrated that patiromer was well tolerated. AEs and SAEs were reported in 60.8% and 8.3% of subjects, respectively, of the overall safety population receiving patiromer for up to 52 weeks. Approximately 20% of subjects receiving patiromer experienced AEs considered related to study drug but no SAEs were considered drug related. Overall, the most common reported AEs were gastrointestinal in nature and predominantly were events of constipation and diarrhea. These events tended to occur early after treatment initiation, were mild to moderate in nature, occurred in less than 10% of subjects, were self-limited and typically did not require dose reductions or discontinuations.

The most common adverse reactions (occurring in ≥ 2% of subjects) in subjects treated with patiromer in the clinical trials were constipation, hypomagnesaemia, diarrhea, nausea, abdominal discomfort, and flatulence. Most adverse reactions were mild to moderate. Constipation generally resolved during the course of treatment. Refer to the current version of the Investigator's Brochure for additional information (Investigator's Brochure, 2016).

Potassium levels < 3.5 mEq/L occurred in approximately 4.7% of subjects and none of these events were serious AEs. Approximately 9% of subjects in clinical trials developed hypomagnesemia with a serum magnesium value < 1.4 mg/dL. AEs of chronic renal failure, acute renal failure and cardiac disorders events were also observed; however, these events generally were not assessed as being attributable to patiromer but consistent with AEs expected in study population with a high burden of CKD, diabetes mellitus, heart failure, and coronary artery disease.

During the clinical studies, the most commonly reported adverse reactions leading to discontinuation of patiromer were gastrointestinal adverse reactions (2.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%) and flatulence (0.5%).

To date, no clinical studies with patiromer have been performed in children.

Refer to the current version of the Investigator's Brochure for a more detailed summary of these clinical studies.

1.3 Rationale

The safety and effectiveness of patiromer has not been evaluated in children. The current study RLY5016-206p is the first study to explore the use of patiromer in children and adolescents 2 – < 18 years of age.

1.4 Rationale for Study Design

Patiromer binds potassium predominantly in the lumen of the colon and increases fecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels. Given its mechanism of action, patiromer is expected to act similarly in adults and children and should be effective in lowering serum potassium levels in pediatric patients with hyperkalemia. Therefore, the current study focuses on patiromer dose finding in the first 14 days of the study followed by an additional 5.5-month safety follow-up.

The pediatric subjects, children and adolescents 2 – < 18 years of age, are divided into three age cohorts (2 – < 6 years, 6 – < 12 years and 12 – < 18 years). The study will commence with the oldest age cohort (12 – < 18 years) and the lowest of three patiromer starting dose levels; this is to ensure safety of younger age subjects who might be the most vulnerable to potential adverse events associated with patiromer. The SMC and DSMC will review safety and PD data from the three initial subjects. If the SMC and DSMC agree that the patiromer starting dose evaluated is appropriate, then nine additional subjects (or fewer if more than three subjects were initially enrolled) will be evaluated at this starting dose level for a total of 12 subjects at the recommended starting dose. If the SMC and DSMC do not agree that the initial patiromer starting dose evaluated is appropriate, then the next higher patiromer starting dose level will be evaluated in three additional subjects. The SMC and DSMC review process and determination of whether the

recommended starting dose was achieved or not will be repeated for these three subjects. Once the recommended patiromer starting dose is determined for a particular age cohort, no additional dose levels will be evaluated. The safety and PD data from the older age cohort will be used by the SMC and DSMC to determine the starting dose for the younger age cohorts. The total sample size could be as low as 36 (three initially treated subjects plus an additional nine if the first dose is chosen as the recommended dose for each of the three different age cohorts) or up to 54 if all three patiromer starting dose levels are studied for each age cohort.

The proposed dosing regimen in adults is once daily administration; the same dosing regimen is proposed for the pediatric population.

1.5 Rationale for Patiromer Starting Doses

The starting doses of patiromer in each age cohort were selected based on the median weights for boys and girls within each of the three age categories using standard growth data (CDC, 2010). The initial weight-based doses selected were guided by the starting dose in adults (8.4 g/day patiromer), a higher commonly used dose in adults (16.8 g/day) and a dose below the adult efficacy range (4.2 g/day patiromer) in the event children have a different response profile than adults.

Patiromer dose titrations up and down are allowed to achieve and maintain potassium in the target range of 3.8 – 5.0 mEq/L. The titrated increment or decrement is planned to be the lowest starting dose for each age group.

2 TRIAL OBJECTIVES

Primary: To assess change from baseline in serum K^+ levels to Day 14 following administration of different doses of patiromer administered once daily in children 2 – < 18 years of age with CKD and hyperkalemia.

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

3 TRIAL DESIGN

3.1 Description

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.

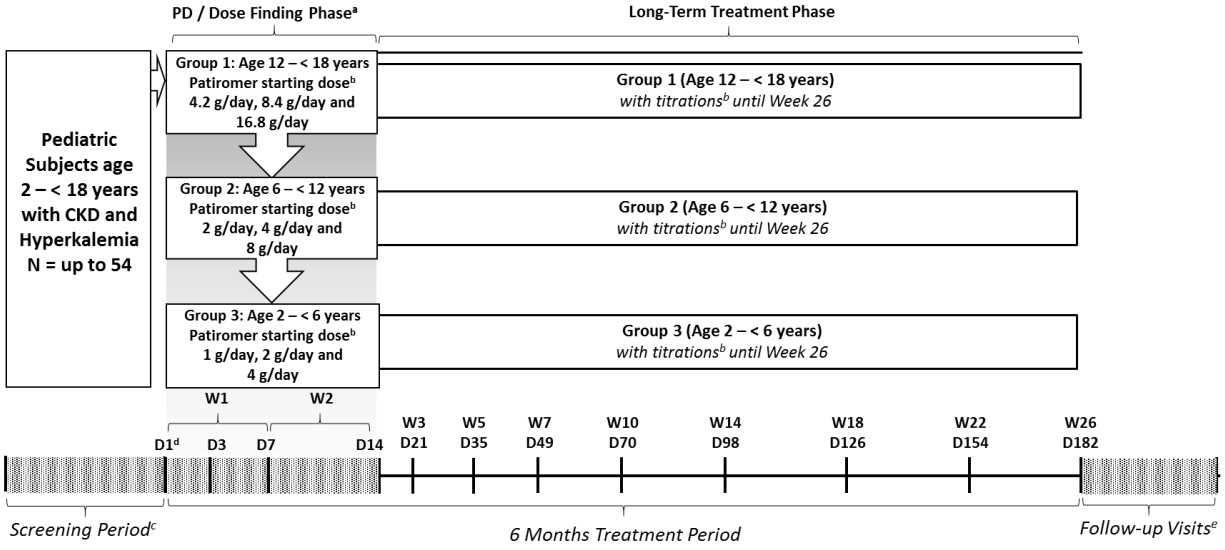
The study will include two treatment phases: PD / Dose Finding Phase consisting of the initial 14-day dose finding period followed by an up to 5.5-month Long-Term Treatment Phase for a total study participation duration for individual subjects of up to 6.5 months (see Figure 1). The overall design of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

3.2 Study Period

3.2.1 Screening Visit(s)

At screening, subjects should arrive in the morning of the Screening Visit(s) and will be assigned a subject identification (Subject ID) number. This will be a unique number generated by the interactive web response system (IWRS). Section 4 lists the inclusion and exclusion criteria for study entry.

Screening (up to 7 Days):

Subject's eligibility will be assessed during a Screening Period with up to two visits (Screening Visit 1, Screening Visit 2). Eligibility for this study requires the presence of hyperkalemia assessed by two blood or serum potassium measurements performed on separate days; qualifying potassium values are 5.1 to < 6.5 mEq/L. A standard of care potassium value measured within 42 days to

2 days prior to Screening may be used for one of the potassium values to assess eligibility. The following scenarios are allowed for obtaining the two qualifying potassium values (5.1 to < 6.5 mEq/L) (see schema in Appendix D):

- For subjects **with a recent standard of care potassium measurement**, the two qualifying potassium values will be the most recent standard of care potassium measurement obtained from 42 days to 2 days prior to Screening Visit 1 and the local potassium measurement at Screening Visit 1
- For subjects **without a recent standard of care potassium** measurement within 42 days to 2 days prior to Screening Visit 1, the first qualifying potassium value will be obtained at Screening Visit 1 and the second at Screening Visit 2, occurring 2 to 7 days after Screening Visit 1

A potassium level of < 5.1 or ≥ 6.5 mEq/L for either screening local potassium value will result in screen failure. Subjects who screen fail may be rescreened once upon the approval of the Medical Monitor; see Section 6.1.3 for details.

For subjects who meet the hyperkalemia eligibility criterion, additional assessments will also be performed at Screening Visit 1 and/or Screening Visit 2 to determine eligibility for study entry (see Section 6.1 and Appendix A for further details).

For subjects who meet all eligibility criteria at either Screening Visit 1 or Screening Visit 2, that visit should be converted to the Day 1 Visit (Baseline). In cases where this is not possible, eligible subjects must return the next day to complete the Day 1 Visit.

Subjects may be re-screened (see Section 6.1.3 for further details).

3.2.2 14-Day PD / Dose Finding Phase:

Eligible subjects will enter a 14-Day PD / Dose Finding Phase consisting of four scheduled visits: Day 1, Day 3, Day 7 and Day 14. Blood or serum potassium concentrations will be measured locally and by the central laboratory at each of the 4 scheduled visits (see Appendix 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). Additional laboratory assays (Appendix C) will be performed at specified visits according to the Schedule of Events (see Appendix A). 12-lead ECG will be performed at Day 3, 7, and 14 Visits if the local K+ is >6.0 mEq/L at that visit.

Eligible subjects will be categorized into three different age cohorts (12 – < 18 years, 6 – < 12 years, and 2 – < 6 years). Enrollment will start with three subjects at the oldest age cohort first; this is to ensure safety of younger age subjects who might be the most vulnerable to potential adverse events associated with patiromer. Initiation of enrollment of subjects in the younger age cohorts will depend on DSMC review (See Section 8.6 for further details).

Up to three starting dose levels will be evaluated in each age group. The initial dose evaluated will be the lowest of the planned starting dose levels for each age group (see Table 1).

Table 1: Planned Patiromer Starting Dose Levels for Each Age Cohort

Age Cohort (years)	Starting Dose Levels (g/day)		
	Lowest	Mid	Highest
12 – < 18	4.2	8.4	16.8
6 – < 12	2	4	8
2 – < 6	1	2	4

Note: the starting doses for the 6 – < 12 years of age and 2 – < 6 years of age cohorts may require modification based upon the DSMC recommendation after their review of the safety and PD data of the older cohorts (see Section 8.6 for further details).

Once the initial group of subjects at a given starting dose level complete their 14-Day PD / Dose Finding Phase, PD and safety data will be provided to the DSMC. The DSMC will evaluate safety and PD data, as well as the number of subjects requiring dose titration. Based on its review, the DSMC will determine if the starting dose for subjects under review was appropriate, in which case, nine additional subjects (or fewer if more than three subjects were initially enrolled) in the same age group will be enrolled at the same starting dose. If the DSMC determines that the starting dose did not result in an acceptable PD response, and the safety is acceptable, the DSMC will provide a recommendation to evaluate the next starting dose in the age group (see Section 8.6 for detailed information on the DSMC).

Subject screening will pause periodically throughout the study to allow for preparation of data and DSMC review and provision of recommendations. Any subjects who are in the Screening Period when the pause is announced may be enrolled provided they meet all eligibility criteria.

Patiromer dose titration is allowed per a protocol-specified algorithm (See Section 5.2.1). The titrated increment or decrement is planned to be the lowest starting dose for each age group.

All patients treated in the PD / Dose Finding Phase will be included in the Long-Term Treatment Phase.

3.2.3 Long-Term Treatment Phase:

After completion of the 14-Day PD / Dose Finding Phase, subjects then enter a Long-Term Treatment Phase that consists of eight visits over a period of 5.5 months. Study visits consist of Week 3, Week 5, Week 7, Week 10, Week 14, Week 18, Week 22 and Week 26 (see Appendix B). Dose adjustments in the Long-Term Treatment Phase may be made at each study visit starting with the Week 2 (Day 14) Visit according to the titration algorithm (see Section 5.2.1).

At each study visit in the Long-Term Treatment Phase, potassium levels will be measured locally and by central laboratory. ECG evaluations will be performed as soon as possible whenever the local K^+ level is > 6.0 mEq/L; at the Week 26 (or ET) Visit, an ECG will be performed regardless of potassium level. Additional laboratory assays and assessments will be performed according to the Schedule of Events (see Appendix B). A full list of central laboratory assays is provided in Appendix C.

Study visits at Week 3, Week 10 and Week 22 are optional and may be omitted under the following circumstances:

- For the Week 3 visit, the local potassium at Day 14 was in the target range (3.8-5.0 mEq/L) and no dose adjustment was made at Day 14

- For the Week 10 and/or Week 22 visits, the local and central potassium were both in the target range (3.8-5.0 mEq/L) at the prior visit (Week 7 and Week 18), respectively

- An unscheduled visit did not occur between the most recent scheduled visit and the planned visit to be omitted (e.g., there must not be an unscheduled visit between Week 7 and Week 10 to omit the Week 10 visit). An exception to this unscheduled visit criterion is an unscheduled visit that is solely for resupply of study drug.

- No dose adjustment in patiromer was made at the prior visit (Day 14, Week 7, Week 18, respectively) and the investigator considers additional dose adjustments to be unlikely based potassium control to date during the study

- The investigator determines that there is no ongoing medical issue that needs follow up prior to the next scheduled visit at Week 5, Week 14, Week 26, respectively

During the Long-Term Treatment Phase, up to 2 non-sequential study visits may be conducted remotely using the Sponsor approved Home Care vendor at certain investigational sites in certain countries. Certain study procedures may be omitted at Home Care Visits (see Section 6.2.5). Home Care visits may not be conducted at the visit just prior or just after an optional visits at Week 3, Week 10 or Week 22 that was skipped. The Week 26 (or ET) visit must occur at the investigational site and may not occur as a Home Care visit.

3.2.4 Follow-up Period

All subjects will enter the Follow-up Period including:

- Subjects who completed the Long-Term Treatment Phase (i.e., attended the Week 26 Visit)
- Subjects who did not complete the Long-Term Treatment Phase and were withdrawn early prior to the Week 26 Visit

The Follow-up Period will consist of one visit at 7 days and one phone call at 14 days after stopping patiromer treatment. The investigator may require the Phone Call Follow-up to be converted into an onsite visit if the potassium level measured during Follow-up Visit at 7 days after stopping patiromer treatment is of concern.

4 SUBJECT SELECTION AND WITHDRAWAL

All potential study subjects will be evaluated using the inclusion and exclusion criteria, described below.

4.1 Inclusion Criteria

Subjects must meet ALL the following criteria:

1. Written assent (when applicable) and written informed consent by a legally authorized representative provided prior to participation in the study

2. Age 2 – < 18 years old (subject's age should not exceed that of the age cohort into which s/he is enrolled for at least the entire 14 days of the PD / Dose Finding Phase)

3. Pediatric subjects with CKD and eGFR < 90 mL/min/1.73 m^2 calculated using the Schwartz formula as described in Section 7.2, including renal transplant subjects, based on local creatinine measurement at Screening

4. Two blood or serum potassium measurements of 5.1 to < 6.5 mEq/L performed on separate days (see Section 6.1)

5. In the opinion of the Investigator, the subject is expected to require treatment for hyperkalemia for at least 6 months

6. If taking any RAASi, beta blockers, fludrocortisone or diuretic medications, must be on a stable dose for at least 28 days prior to Screening

7. Females of child-bearing potential must be non-lactating, must have a negative pregnancy test at Screening, and must have used an effective form of contraception (e.g., abstinence, hormonal, chemical, physical barrier, etc.) for at least 1 month before patiromer administration. Subjects of child-bearing potential must agree to continue using contraception throughout the study and for 1 month after the last dose of patiromer

4.2 Exclusion Criteria

Subjects must NOT meet ANY of the following exclusion criteria:

1. Subjects with pseudohyperkalemia due to hemolysis or to abnormally high numbers of platelets (> 500,000/mm^3), leukocytes (> 70,000/mm^3), or erythrocytes (hematocrit > 55%) at Screening based on results obtained locally

2. Any subject with evidence of potential potassium-related ECG changes (i.e., changes consistent with hyper- or hypokalemia) at Screening

3. Any of the following renal conditions: maintenance hemodialysis or peritoneal dialysis, renal artery stenosis, and acute kidney injury (defined by 2012 Kidney Disease Improving Global Outcomes (KDIGO, 2012) or a history of acute renal insufficiency in the past 3 months

4. A history of or current diagnosis of a severe gastrointestinal diagnosis or surgery that could affect gastrointestinal transit of the drug (e.g. a severe swallowing disorder, uncorrected pyloric stenosis, intussusception, any other intestinal obstruction [e.g. Hirschsprung disease,

chronic intestinal pseudo-obstruction, clinically significant postsurgical abdominal adhesions] or any gut-shortening surgical procedure prior to Screening)

5. A history of or current diagnosis of a condition that in the opinion of the investigator increases the risk of aspiration of patiromer if it will be given orally

6. Liver enzymes ALT, AST > three times upper limit of normal at Screening, based on the local laboratory ALT and AST

7. Active cancer, currently on cancer treatment or history of cancer in the past 2 years (except for non-melanoma skin cancer)

8. Heart or liver transplant recipient, or anticipated need for transplant during the study Treatment Period, including a scheduled kidney transplant recipient (note: patients currently on a kidney transplant wait list are not excluded unless there is an identified donor)

9. Chronic alcohol abuse or substance use disorder within 1 year of Screening

10. Subjects currently being treated with or having taken any one of the following medications (includes resins) in the 7 days prior to Screening: sodium or calcium polystyrene sulfonate, sodium zirconium cyclosilicate, and drospirenone

11. Use of the following medications if doses have not been stable for at least 14 days prior to Screening or if doses are anticipated to change during the 14-day PD / Dose Finding Phase:

    - digoxin;
    - bronchodilators;
    - theophylline;
    - heparins (including low molecular heparins);
    - canagliflozin;
    - tacrolimus;
    - mycophenolate mofetil;
    - cyclosporine
    - trimethoprim or cotrimoxazole

12. Use of any investigational product for an unapproved indication within 30 days prior to Screening or within 5 half-lives, whichever is longer

13. Known hypersensitivity to patiromer or its components

14. In the opinion of the Investigator, inability to comply with the protocol

15. In the opinion of the Investigator, any medical condition, uncontrolled systemic disease, or serious intercurrent illness that would significantly decrease study compliance or jeopardize the safety of the subject or potentially affect the quality of the data such as: hyperkalemia at Screening that requires emergency intervention; cardiovascular event or intervention within 3 months prior to Screening; a hemodynamically unstable arrhythmia; hospitalization for heart failure within the past 3 months; poorly controlled BP; poorly controlled diabetes mellitus or frequent need for adjustment in insulin prescription or recent hospitalization for treatment of hyper or hypoglycemia

4.3 Subject Withdrawal

Within the provisions of informed consent and assent (if required) and good clinical judgment with respect to the subject's safety, every attempt should be made to have subjects complete both Treatment Periods and Follow-up Period. Subjects and subject's legally authorized representatives will be informed that they are free to withdraw from the study at any time. The Investigator and/or the Medical Monitor may exercise his or her medical judgment to terminate a subject's participation in the study because of clinically significant changes in any clinical or laboratory parameter. If the Investigator is concerned regarding any potassium value, a re-test of potassium level and/or ECG evaluation for electrophysiological consequences can be initiated by the Investigator at his/her discretion.

On an ongoing basis, the investigator will monitor the degree of burden of participation in the study as well as the associated risk. Participation in this study should only be continued if the investigator determines there is no more than a minimal increase over the burden and risk that are described in the protocol or associated with routine clinical examinations, clinical care and treatment of patients with chronic kidney disease and hyperkalemia.

All subjects withdrawn early from the study for any reason will be followed for safety for 2 weeks after receiving the last dose of patiromer. Subjects who meet any of the following criteria at any time during the study must be withdrawn from the study and should be medically managed as per standard of care by the Investigator:

- Serum magnesium < 1.0 mg/dL (< 0.41 mmol/L) confirmed by re-test
- Potassium-related ECG changes
- Treatment-related SAE (SAE form must be completed)
- Pregnancy (pregnancy form must be completed)
- Withdrawal of assent by subject (if required) or informed consent by legally authorized representative

Other reasons for withdrawal may include:

- Adverse Event
- Protocol deviation
- Subject's non-compliance: poor compliance with study treatment

- Investigator's decision (e.g., in the Investigator's judgment discontinuation is in the subject's best interest; e.g., need for prohibited medication)
- Subject is lost to follow-up: the subject did not return for visits and study personnel were unable to contact the subject
- Subject transitions to dialysis during the study and does not require additional patiromer treatment (see Section 4.4 for details)
- Other: the subject's participation in the study was terminated for a reason other than those listed above. The Investigator must specify the detailed reason.

In addition, a variety of reasons may lead either Relypsa or a regulatory agency to terminate the study early, in which case all subjects would be withdrawn from the study.

It is important to collect information explaining why subjects withdrew from the study. This information, together with AEs occurring at those times, may be very informative of the cause-specific reasons for why some subjects remain in the study or on the assigned treatment while others do not. Therefore, although the subject's legally authorized representatives are not obliged to give their reason for withdrawing consent, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subjects' rights. Reasons for withdrawal of consent, when provided by the subject's legally authorized representatives, will be recorded in the electronic case report form (eCRF). The procedures described for Early Termination (ET, see Section 6.4) will be performed, if possible. Every effort will be made to contact the legally authorized representatives of a subject who fails to attend a study visit, or does not respond by telephone, in order to ensure that the subject is in satisfactory health. The Investigator will immediately inform the Medical Monitor of removal or early withdrawal of a subject from the study.

If a subject withdrew within the 14-Day PD / Dose Finding Phase, the DSMC may be consulted regarding possibility of replacing the withdrawn subject.

4.4 Dialysis

The medical monitor should be contacted prior to enrolling a subject if it is anticipated that subject will transition to dialysis any time during the study. In addition, the medical monitor should be consulted when the investigator determines that an enrolled subject will require dialysis. Patients who are anticipated to require dialysis shortly after enrollment (within 6-8 weeks of Day 1) may not be suitable for enrollment due to unstable medical status and fluctuating potassium levels. In most cases for subjects who transition to maintenance hemodialysis or peritoneal dialysis during the study patiromer should be discontinued as soon as feasible. Continuation of patiromer (including a dose of 0 g/day) may be allowed for patients transitioning to dialysis under the following conditions:

- The Investigator determines continuation of patiromer may be needed to control hyperkalemia; (documentation of medical justification must be provided)

- Agreement to follow additional guidance for potassium monitoring (to be provided as needed)

- Approval by the medical monitor

Alternative strategies to control hyperkalemia (e.g., adherence to low potassium diet, dialysis prescription) should be utilized to facilitate withdrawal of patiromer and management of hyperkalemia once patiromer is discontinued.

Dialysis sessions conducted during the study should be documented in eCRF. Subjects who undergo dialysis and discontinue patiromer should be withdrawn from the study. Subjects on a patiromer dose of 0 g/day should be withdrawn from the study once the investigator determines patiromer will no longer be required. Any subject discontinuing the study early should complete the Early Termination visit (see Section 6.4) and the follow up visits.

5 STUDY TREATMENTS

5.1 Treatment Blinding

The study is open-label and non-randomized.

5.2 Allocation to Treatment

At the Baseline Visit, the IWRS will assign all subjects who meet the entry criteria to their patiromer starting dose. Enrollment will start with the oldest age cohort (age 12 – < 18 years) first, followed by the cohort aged 6 – < 12 years, and subsequently the youngest cohort aged 2 – < 6 years of age. Up to three starting dose levels will be evaluated in each age group. The initial dose evaluated will be the lowest of the planned starting dose levels for each age group.

The planned starting dose levels of patiromer for each age cohort are:

- Age 12 – < 18 years: 4.2 g/day, 8.4 g/day and 16.8 g/day
- Age: 6 – < 12 years: 2 g/day, 4 g/day and 8 g/day
- Age: 2 – < 6 years: 1 g/day, 2 g/day and 4 g/day

Note: the starting doses for the 6 – < 12 years of age and 2 – < 6 years of age cohorts may require modification based upon the DSMC recommendation after their review of the safety and PD data of the older cohorts (see Section 8.6 for further details).

5.2.1 Patiromer Titration

Patiromer dose titration is allowed during study visits to achieve and maintain K^+ levels in the 3.8 – 5.0 mEq/L range. Titrations will be based on potassium levels measured locally and per the protocol-specified algorithm.

Patiromer dose adjustments are planned to be made in increments or decrements that represent the lowest starting dose of patiromer for each age group. Specifically, the following dose adjustments are allowed:

- For subjects Age 12 – < 18 years: titrations up or down by 4.2 g/day
- For subjects Age 6 – < 12 years: titrations up or down by 2 g/day
- For subjects Age 2 – < 6 years: titrations up or down by 1 g/day

The DSMC may adjust the titration algorithm for each age cohort after their review of PD and Safety data from the previously enrolled subjects. The maximum dose of patiromer is 25.2 g/day during the study. For subjects in the 2 – < 6 year and 6 – < 12 year age groups the highest anticipated doses are 7 g/day and 14 g/day, respectively; the DSMC may modify these doses for these age groups based on review of safety and PD data (See section 8.6).

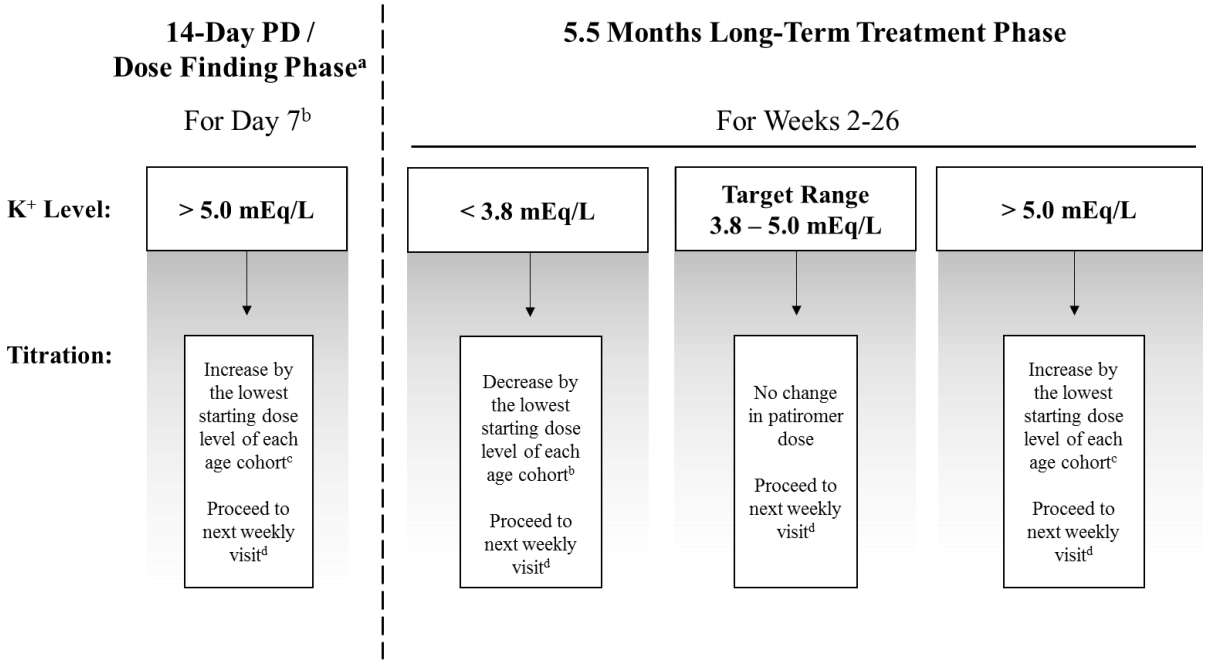
During the 14 Day PD / Dose Finding Phase, patiromer dose up-titration by the permitted titration increment for each age group is allowed beginning at Day 7 for K^+ value > 5.0 mEq/L. Dose titration may not be required if the potassium decrease from the previous visit was ≥ 0.5 mEq/L. Patiromer dose down-titration by the permitted titration decrement for each age group or more is allowed for any K^+ value < 3.8 mEq/L to a minimum patiromer dose of 0 g/day. If patiromer dose requires titration, then initiation of the titrated patiromer dose should occur at the next planned administration.

Day 3 Safety Assessment: As a safety measure to ensure that subject exposure to hyperkalemia is not prolonged, the patiromer dose may be up-titrated at Day 3 only if the K^+ level is ≥ 5.5 mEq/L and is greater than the most recent locally obtained screening potassium value. 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).

During the Long-Term Treatment Phase, patiromer dose up-titration by the permitted titration increment for each age group is allowed for any K^+ value > 5.0 mEq/L. Dose titration may not be required if the potassium decrease from the previous visit was ≥ 0.5 mEq/L. Patiromer dose down-titration by the permitted titration decrement for each age group, or more, is allowed for any K^+ value < 3.8 mEq/L to a minimum patiromer dose of 0 g/day. If patiromer dose requires titration, then initiation of the titrated patiromer dose should occur at the next planned administration.

A description of the patiromer dose titration algorithm for each age group is described in Figure 2 below.

Figure 2: Planned Patiromer Dose Titration Algorithm.



[a] At Day 3, as a safety measure to ensure that subject exposure to hyperkalemia is not prolonged, patiromer dose may be up-titrated only if the K^+ level is ≥ 5.5 mEq/L and is greater than the most recent locally obtained screening potassium value. 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] Down titration of patiromer dose by the designated decrement for each age cohort or more is allowed for any K^+ values < 3.8 mEq/L to a minimum patiromer dose of 0 g/day. If patiromer dose requires titration, then initiation of the titrated patiromer dose should occur at the next planned administration.

[c] Dose titration may not be required if the potassium decrease from the previous visit was ≥ 0.5 mEq/L.

[d] If patiromer dose requires titration, then initiation of the titrated patiromer dose should occur at the next planned administration. Subjects are required to return for a Mandatory Safety Visit within 7 days if the next scheduled study visit is > 1 week after a dose increase has been initiated. Unscheduled visits may occur during any phase of the study at the discretion of the Investigator. Refer to Section 6.5.1 for additional information and criteria for Mandatory Safety Visits.

5.3 Drug Supplies

5.3.1 Formulation and Packaging

Patiromer will be provided open-label to subjects as a powder for oral suspension in packets with appropriate labeling. The individual packets will be assembled as a kit for dispensing the adequate amount of patiromer for each subject. Each packet inside an individual kit will contain either 4.2 g patiromer, 2.0 g or 1.0 g patiromer. Subject's legally authorized representative will be instructed to mix patiromer with water, apple juice, or cranberry juice. Patiromer shipped to study site should be stored refrigerated (2 – 8°C). Study subject's legally authorized representatives will be instructed to store patiromer refrigerated (2 – 8°C) for the duration of the study.

Refer to the current version of the Investigator's Brochure for a more detailed description of the investigational drug.

5.3.2 Preparation and Dispensing of Patiromer

Patiromer is for oral administration. The subject's legally authorized representative and the subject will be instructed to mix patiromer with water, apple juice, or cranberry juice. Each patiromer dose should be individually prepared under the supervision of the subject's legally authorized representative immediately prior to administration.

Patiromer should not be heated (e.g., microwaved) or added to heated foods or liquids. Patiromer should not be taken in its dry form but mixed with water, apple, or cranberry juice only. Patiromer doses should be prepared following the steps below:

- Measure the initial volume of water (or cranberry or apple juice) needed for the assigned daily dose, see Table 2, Table 3, and Table 4 for details. Pour the initial volume of the water (or cranberry or apple juice) into a cup or glass, then add patiromer and stir. Add the additional volume of the water (or cranberry or apple juice) and stir thoroughly. The powder will not dissolve and the mixture will look cloudy. Add more water (or cranberry or apple juice) to the mixture as needed for desired consistency
- Drink the mixture immediately. If powder remains in the cup or glass after drinking, add more water (or cranberry or apple juice), stir and drink immediately. Repeat as needed to ensure the entire dose is administered. Subjects and their legally authorized representative will be instructed that patiromer can be taken either with or without food

Consult the Pharmacy Manual for details on patiromer administration through an enteral feeding tube.

Table 2: Mixing Volumes for 12 – < 18 Years Age Group Patiromer Doses (4.2 g Packets)

Possible Daily Doses[a] (g/day patiromer)	Initial Volume per Dose (mL) (Step 1)	Additional Volume (mL) (Step 2)	Total Volume (mL)
4.2 (1 packet)	15	30	45
8.4 (2 packets)	15	30	45
12.6 (3 packets)	30	60	90
16.8 (4 packets)	30	60	90
21.0 (5 packets)	30	60	90
25.2 (6 packets)	30	60	90

[a] Doses described include starting doses and potential escalated doses.

Table 3: Mixing Volumes for 6 – < 12 Years Age Group Patiromer Doses (2 g Packets)

Possible Daily Doses[a] (g/day patiromer)	Initial Volume per Dose (mL) (Step 1)	Additional Volume (mL) (Step 2)	Total Volume (mL)
2 (1 packet)	5	10	15
4 (2 packets)	10	20	30
6 (3 packets)	15	30	45
8 (4 packets)	15	30	45
10 (5 packets)	30	60	90
12 (6 packets)	30	60	90
14[b] (7 packets)	30	60	90

[a] Doses described include starting doses and potential escalated doses.

[b] Equivalent to the adult dose of 25.2 g/day based on weight-based scaling.

Table 4: Mixing Volumes for 2 – < 6 Years Age Group Patiromer Doses (1 g Packets)

Possible Daily Doses[a] (g/day patiromer)	Initial Volume per Dose (mL) (Step 1)	Additional Volume (mL) (Step 2)	Total Volume (mL)
1 (1 packet)	2.5	5	7.5
2 (2 packets)	5	10	15
3 (3 packets)	5	10	15
4 (4 packets)	10	20	30
5 (5 packets)	15	30	45
6 (6 packets)	15	30	45
7[b] (7 packets)	15	30	45

[a] Doses described include starting doses and potential escalated doses.

[b] Equivalent to the adult dose of 25.2 g/day based on weight-based scaling.

The Investigator or qualified designee will be responsible for dispensing patiromer and for documenting the date dispensed, lot number, study visit, and subject identification number on the appropriate drug accountability records at the time of dispensation.

5.3.3 Dosing and Administration of Patiromer

Subjects should arrive in the morning of the Screening Visit(s), if possible, since dosing with patiromer may be initiated on the same day as the Screening visit. Patiromer will be administered QD and doses should be taken approximately 24 hours apart. In this study, there should be a 3 hours separation between patiromer dosing and that of other oral medications; certain medications may be co-administered with patiromer at the discretion of the Investigator (see Section 5.5). Subjects and their legally authorized representative will be instructed that patiromer can be taken with or without food.

Patiromer dose titration is allowed per a protocol-specified algorithm to achieve and maintain potassium levels (measured locally) within the target range of 3.8 – 5.0 mEq/L. A description of the patiromer dose titration algorithm is provided in Section 5.2.1.

If patiromer dose requires titration, then initiation of the titrated patiromer dose should occur at the next planned administration. The last dose of patiromer for all subjects in the study will be taken on the day before the Week 26 Visit (see Appendix B).

All subjects will be provided with a Subject Dosing Diary at Day 1. Subjects and their legally authorized representative will be instructed how to document each patiromer dose and to bring back the Diary for the Investigator and/or designee to review at Day 3, Day 7 and Day 14. The Investigator and/or designee will collect the completed Diary at Day 14.

Note: If the Investigator determines a Day 3 Visit is not needed for a subject whose last screening K^+ is < 5.5 (see Section 6.2.2), then the Diary will only be reviewed at Day 7 and Day 14 Visits.

5.3.4 Compliance

Subject's legally authorized representative will be trained at the Screening / Day 1 Visit and retrained at subsequent visits regarding proper dosing and preparation of patiromer to encourage compliance.

Study staff will assess compliance at every study visit after dispensation to confirm that the subject is taking patiromer according to the protocol instructions and document compliance in the eCRF as detailed in the electronic data capture (EDC) completion guidelines. Compliance will be assessed on the basis of treatment group assignment and on the assigned patiromer dose, duration of treatment and quantity of dispensed and returned kits/packets (used and unused).

5.4 Investigational Product Storage and Accountability

The Investigator or designee will verify and acknowledge receipt of patiromer. Patiromer must be stored in a secure area under the proper storage requirements with access restricted to the Investigator or designees. No subject other than those enrolled in this specific investigation shall take patiromer designated for this clinical study. Patiromer may not be utilized for any laboratory or animal research. Patiromer dispensed to subjects must be accurately recorded on the Drug Accountability Record maintained at the Study Center. Subject's legally authorized representatives should be instructed to return all investigational product dispensed to them (used and unused kits/packets) at each study visit.

All used and unused kits/packets of patiromer will be retained at the site for Study Monitor's verification.

Patiromer should be shipped and stored under refrigeration (2 – 8°C) in a secure location.

5.5 Concomitant Medications

Information on all concomitant medications (prescription, over-the-counter, herbal and naturopathic remedies, etc.) will be collected beginning at the Screening Visit and continuing for the duration of the study (including ET) until the last study visit.

The use of magnesium supplementation is allowed during the study and should be considered for subjects whose serum magnesium is near or below the lower limit of normal.

Patiromer should be taken 3 hours before or 3 hours after administration of other concomitant medications. At the discretion of the Investigator, the following drugs may be coadministered with patiromer: allopurinol, amlodipine, amoxicillin, apixaban, aspirin, atorvastatin, cephalexin, cinacalcet, clopidogrel, digoxin, furosemide, glipizide, lisinopril, lithium, metoprolol, phenytoin, rivaroxaban, spironolactone, trimethoprim, valsartan, verapamil, and warfarin.

For subjects taking phosphate binders TID and for whom in the opinion of the Investigator one dose per day of the phosphate binder can be replaced by patiromer, patiromer may be dosed with the same meal each day and the phosphate binder dosed with two other meals each day.

In general, subjects should continue on regular doses of their usual medications, including non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, bronchodilators and theophylline, laxatives, and contraceptives. Doses of these medications should be kept as stable as possible during the study. Medications that the Investigator deems indicated for treatment of any intercurrent illness or a pre-existing condition that do not form an exclusion criterion for participation in this study are generally allowed. If new medications for mild to moderate pain relief are required, it is preferred that NSAIDs and COX-2 inhibitors are avoided and alternatives such as acetaminophen are used.

For subjects taking medications with a narrow therapeutic index, careful monitoring is advised.

5.5.1 Permitted Antihypertensive Medications and Medications for Heart Failure

5.5.1.1 RAAS inhibitor Medications, Digitalis Glycosides and Diuretics

For subjects taking any RAAS inhibitor medications or diuretic medications, the dose of these medications must be stable for at least 28 days prior to Screening. The use of digitalis glycosides (such as digoxin) are permitted if the subject has been on a stable dose at least 14 days prior to Screening.

14-Day PD / Dose Finding Phase

During subject's participation in the 14-day PD / Dose Finding Phase of the study, no new RAAS inhibitor medications, digitals glycosides or diuretics should be initiated and doses of concomitant RAAS inhibitor medications, digoxin and diuretics should not be changed. In the event that the dose of the RAAS inhibitor, digoxin or potassium-sparing diuretic needs to be adjusted during the 14-day PD / Dose Finding Phase the subject may need to be early withdrawn from the study and the Medical Monitor should be contacted prior to a final decision regarding the discontinuation of patiromer.

Recommendations regarding the timing of any medication as described in Section 5.5 should be followed to minimize the possibility of a drug interaction. Clinical response and/or blood levels where possible should be monitored as higher doses may be required during concomitant treatment with patiromer.

Long-Term Treatment Phase

During the subject's participation in the Long-Term Treatment Phase, if needed, adjustments to RAAS inhibitor medications, digitalis glycosides or diuretics are permitted. However, if the subject is prescribed non-RAAS inhibitor antihypertensive medications or non-potassium sparing diuretics every effort should be made to adjust the non-RAAS inhibitor medication or non-potassium sparing diuretics prior to adjusting the RAAS inhibitor medications or potassium-sparing diuretics.

If at any time during the study a subject develops symptomatic postural hypotension, or subject's BP is too low in the opinion of the Investigator, non-RAAS inhibitor antihypertensive treatments should either be removed, or their doses reduced before adjustments are made to the RAAS inhibitor medications for patients taking these medications. If hypotension persists after reducing or discontinuing non-RAAS inhibitor antihypertensive medications in the Long-Term Treatment Phase, it is acceptable to alter RAASi medications per the Investigator's discretion.

Recommendations regarding the timing of any medication as described in Section 5.5 should be followed to minimize the possibility of a drug interaction. Clinical response and/or blood levels where possible should be monitored as higher doses may be required during concomitant treatment with patiromer.

Increases in potassium levels may occur as early as 2 days after discontinuation of patiromer, which may be more likely in subjects who continue taking RAASi medications after stopping patiromer. In the Follow-Up Phase, an unscheduled visit may occur at the investigator's discretion for measurement of potassium level (See Section 6.5.1).

5.5.1.2 Other Antihypertensive Medications and Medications for Heart Failure

The use of beta-adrenergic blockers (bisoprolol, sustained release metoprolol and carvedilol are the preferred beta-adrenergic blockers but are not required) and diuretics are permitted if the subject has been on a stable dose at least 28 days prior to Screening. However, recommendations regarding the timing of any medication as described in Section 5.5 should be followed to minimize the possibility of a drug interaction. For all medications, clinical response should be monitored as higher doses may be required during concomitant treatment with patiromer (see Section 5.5).

In order to control BP at any time during the study, non-RAAS inhibitor, non-potassium sparing diuretics and antihypertensive drugs that do not affect potassium levels (e.g., calcium channel blocker, alpha blocker and alpha-2 agonist) may be added or modified per the Investigator's discretion.

While every effort should be made to keep the above medications stable during the entire study, doses may be adjusted at the discretion of the Investigator. Subjects being treated with a diuretic and who are not on a consecutive daily dosing regimen and who are scheduled to take a dose of the diuretic on the day of the study visit must be instructed to take their diuretic dose after the local and

central laboratory blood has been drawn for potassium evaluation. Additional medications that are permitted to treat the symptoms or complications of heart failure are aspirin, hydralazine, and nitrates. Doses of these medications do not need to have been stable prior to screening and can be adjusted during the study.

5.5.2 Permitted Medications for Anti-Rejection of Transplant

Subjects treated with tacrolimus, mycophenolate mofetil or cyclosporine should be on a stable dose for at least 14 days prior to Screening and expected to remain on the stable dose during the PD / Dose Finding Phase (first 14 days) of the study. In the event that the dose of the anti-rejection medication requires adjustment during the 14-Day PD / Dose Finding Phase, the study Medical Monitor should be contacted to determine if discontinuation of patiromer and potential early termination from the study is required. Small changes in dose during the 14-Day PD / Dose Finding Phase may be acceptable. During the Long-term Treatment Phase, dose adjustments of tacrolimus, mycophenolate mofetil or cyclosporine are allowed at the discretion of the Investigator.

Recommendations regarding the timing of any medication as described in Section 5.5 should be followed to minimize the possibility of a drug interaction. Clinical response and/or blood levels where possible should be monitored as higher doses may be required during concomitant treatment with patiromer.

5.5.3 Permitted Prophylactic Trimethoprim Antibiotic

Trimethoprim (including cotrimoxazole) used for prophylaxis of infections (e.g., Pneumocystis carinii pneumonia, urinary tract infection) is permitted provided the dose has been stable for 14 days prior to Screening and is expected to remain stable during the 14-Day PD / Dose Finding Phase.

5.5.4 Permitted Fludrocortisone

Fludrocortisone use is permitted provided that the subject has been on a stable dose at least 28 days prior to screening and the dose is expected to remain stable during the 14-day PD / Dose Finding Phase. In the event that prescription for fludrocortisone requires adjustment during the 14 Day PD / Dose Finding Phase, the study Medical Monitor should be contacted. During the Long-Term Treatment phase, investigators should avoid making changes in fludrocortisone dose; however, changes in this medication are acceptable for safety reasons (e.g., hypokalemia, increase blood pressure, edema). For subjects taking fludrocortisone who experience hypokalemia, the investigator should adjust fludrocortisone dose prior to making changes in the patiromer dose if possible, giving due consideration to patient safety and the degree of hypokalemia.

5.6 Prohibited Medications

During the 14-day PD / Dose Finding Phase, the following medications will be prohibited:

- sodium or calcium polystyrene sulfonate
- sodium zirconium cyclosilicate
- drospirenone

During the Long-Term Treatment Phase, the following medications will be prohibited:

- sodium or calcium polystyrene sulfonate
- sodium zirconium cyclosilicate
- drospirenone

6 TRIAL PROCEDURES

Refer to the Schedule of Events (see Appendix A and Appendix B) for the frequency and timing of the required study assessments.

Laboratory-related eligibility criteria will be based on values obtained locally, specifically potassium, creatinine, ALT/AST, CBC, and pregnancy test (females of child-bearing potential). The central laboratory results will be used for the establishment of baseline values, safety, and for all statistical analyses.

The Investigator should base decisions related to potassium (e.g., patiromer titration) on the values obtained locally at the study site only. Central laboratory potassium results will be used for the efficacy analyses and, for the purpose of the Investigator, as supplemental safety information. Central laboratory potassium results should not override any decisions made by the Investigator based on local potassium measurements.

The Investigator must review all laboratory and any ECG results as soon as possible after the results are available. Of particular importance are the timely identification of any out-of-range potassium laboratory results. If the Investigator is concerned regarding any potassium value, a re-test of potassium level and/or ECG evaluation for electrophysiological consequences can be initiated by the Investigator at his/her discretion.

To avoid hemolysis of samples, specimen collection and handling must strictly follow specific instructions provided in the Laboratory Manual. Blood samples for potassium assessment (local and central laboratory) should be collected at approximately the same time (preferably in the morning) for the same subject at all Study Visits (Sections 6.1 and 6.2).

6.1 Screening Visit(s)

Before any study-specific procedures are performed, the legally authorized representative and subject must receive an explanation of all study procedures that is described using age appropriate language. The legally authorized representative must sign and date a written informed consent form (ICF) and the subject must sign and date the assent (when applicable) approved by an institutional review board (IRB) or Ethics Committee (EC) (see Section 12.1 for additional requirements). The timing of the Screening Visit (and all subsequent visits) should take into account planned absences at the research facility and the need for study visits according to the Schedule of Events (see Appendix A and Appendix B).

The subject will be assigned a unique study subject identification number, which will be generated during Screening Visit registration in IWRS.

Subject's eligibility will be assessed during a Screening Period with up to two visits (Screening Visit 1, Screening Visit 2). Eligibility for this study requires the presence of hyperkalemia assessed by two blood or serum potassium measurements performed on separate days; qualifying potassium values are 5.1 to < 6.5 mEq/L. A standard of care local potassium value measured within 42 days to 2 days prior to Screening may be used for one of the potassium values to assess eligibility. The following scenarios are allowed for obtaining the two qualifying potassium values (5.1 to < 6.5 mEq/L):

- For subjects **with a recent standard of care potassium measurement**, the two qualifying potassium values will be the most recent standard of care potassium measurement obtained from 42 days to 2 days prior to Screening Visit 1 and the local potassium measurement at Screening Visit 1
- For subjects **without a recent standard of care potassium** measurement within 42 days to 2 days prior to Screening Visit 1, the first qualifying potassium value will be obtained at Screening Visit 1 and the second at Screening Visit 2, occurring 2 to 7 days after Screening Visit 1

Subjects who screen fail may be rescreened once upon approval of the Medical Monitor, see Section 6.1.3 for details.

For subjects who meet all eligibility criteria at either Screening Visit 1 or Screening Visit 2, that visit should be converted to the Day 1 Visit (Baseline). In cases where this is not possible, eligible subjects must return the next day to complete the Day 1 Visit.

6.1.1 Subjects with Standard of Care Potassium Measurement

Subjects are requested to arrive in the morning of **Screening Visit 1**. The blood specimen obtained will be used to measure potassium locally (a serum sample from the specimen will be sent to the central laboratory for subjects with confirmed eligibility). The following screening activities will be performed at **Screening Visit 1**:

- Legally authorized representative informed consent and subjects' assent (when applicable) signing
- Subject's registration in IWRS
- Review of inclusion and exclusion criteria
- Demographics
- Review of medical history
- Physical examination
- Body weight and height
- Vital Signs (resting heart rate and sitting BP)
- 12-Lead ECG
- Blood or serum potassium levels measured locally

- Blood or serum chemistry tests including AST, ALT, magnesium, creatinine and eGFR measured locally
- Local hematology (CBC including WBC, RBC, hemoglobin, hematocrit, and platelet count)
- Local urine pregnancy test (female subjects of child-bearing potential only). A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result
- AE assessment
- Concomitant medication assessment

The Investigator shall review all screening information as soon as possible for safety and eligibility. Subjects who meet all eligibility criteria should have their **Screening Visit 1** converted to the Day 1 (Baseline Visit) where the starting dose of patiromer is administered to the subjects if scheduling allows. In cases where this is not possible, eligible subjects must return the next day to complete the Day 1 Visit.

6.1.2 Subjects without Standard of Care Potassium Measurement

6.1.2.1 Screening Visit 1

The following screening activities will be performed at **Screening Visit 1**:

- Legally authorized representative informed consent and subjects' assent (when applicable) signing
- Subject's registration in IWRS
- Blood or serum potassium levels (measured locally)
- Demographics
- Medical history (can be performed at Screening Visit 1 or Screening Visit 2)
- Physical Examination (can be performed at Screening Visit 1 or Screening Visit 2)
- Height (can be measured at Screening Visit 1 or Screening Visit 2)
- Vital Signs (resting heart rate and sitting BP)
- 12-Lead ECG (can be measured at Screening Visit 1 or Screening Visit 2)
- AE assessment
- Concomitant medication assessment

6.1.2.2 Screening Visit 2

Subjects with confirmed eligibility for hyperkalemia (a local potassium level of 5.1 to < 6.5 mEq/L) from Screening Visit 1 will be requested to return 2 to 7 days after Screening Visit 1 for Screening Visit 2. Subjects should arrive in the morning of **Screening Visit 2**. The blood specimen obtained will be used to measure potassium locally (a serum sample from the specimen will be sent to the central laboratory for subjects with confirmed eligibility).

The following screening activities will be performed at **Screening Visit 2**:

- Subject's registration in IWRS
- Review of inclusion and exclusion criteria
- Body weight
- Vital Signs (resting heart rate and sitting BP)
- Blood or serum potassium levels measured locally
- Blood or serum chemistry tests including AST, ALT, magnesium, creatinine and eGFR measured locally
- Local hematology (CBC including WBC, RBC, hemoglobin, hematocrit, and platelet count)
- Local urine pregnancy test (female subjects of child-bearing potential only). A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result or if the subject is anuric
- AE assessment
- Concomitant Medication Assessment

The Investigator shall review all screening information as soon as possible for safety and eligibility. Subjects who meet all eligibility criteria should have their Screening Visit 2 converted to the Day 1 (Baseline Visit) where the starting dose of patiromer is administered to the subjects if scheduling allows. In cases where this is not possible, eligible subjects must return the next day to complete the Day 1 Visit.

6.1.3 Re-screening of Subjects

Re-screening will be allowed for subjects who screen fail after approval by the Medical Monitor. A subject may only be re-screened one time.

To re-screen a subject:

- The Medical Monitor must be contacted for re-screening approval
- The subject's legally authorized representative must be re-consented and assent (if required) must be re-obtained
- The subject must receive a new subject identification number assigned by IWRS.
- All screening evaluations must be repeated (see Section 6.1)
- All inclusion and exclusion criteria must be met (see Section 4)

6.2 Treatment Period

6.2.1 Day 1 Visit (Baseline)

The following baseline assessments will be performed for subjects who meet all eligibility criteria (Section 6.1, Appendix A):

- Subject's visit registration in IWRS
- Central laboratory tests (see Appendix C):
- Serum potassium
- Serum chemistry
- Plasma parathyroid hormone
- Serum fluoride
- Urinalysis (not required for anuric subjects, see section 7.2)
- Hematology (CBC)
- Local urine and central serum pregnancy test (female subjects of child-bearing potential only)
- Patiromer dispensation, administration (if possible based on individualized administration time as described in Section 5.5; first dose only)
- Patiromer palatability assessments for subjects ≥ 6 years of age who consume patiromer at the site
- Train parents or representative and, if applicable, subjects on patiromer dosing (including preparation, accountability and compliance)
- Provide parents or representative and, if applicable, subjects with study materials (i.e., Subject Dosing Diary, dosing instructions and emergency card)
- Assessment of AEs
- Assessment of concomitant medications
- Next visit scheduling

6.2.2 Day 3 Visit

Patiromer dose may be adjusted on the Day 3 Visit based on the potassium level measured locally according to the titration algorithm. A description of the patiromer dose titration algorithm is provided in Section 5.2.1.

At the discretion of the Investigator, the Day 3 Visit is optional for subjects whose most recent Screening local K^+ is < 5.5 mEq/L.

The Day 3 Visit is mandatory for subjects whose most recent Screening local K^+ is ≥ 5.5 mEq/L.

The activities for Day 3 (± 1 day) are detailed below and in Appendix A:

- Subject's visit registration in IWRS
- Vital Signs (resting heart rate and sitting BP)
- 12-Lead ECG (Only if local K+ is > 6.0 mEq)

- Blood or serum potassium levels (measured locally) and serum potassium measured by central laboratory
- Patiromer dose down titration if needed (see Section 5.2.1)
  Note: Patiromer dose up titration may occur only if the K^+ level is ≥ 5.5 mEq/L and greater than the most recent locally obtained screening potassium value
- Patiromer dispensation, reconciliation, accountability, compliance, and subject retraining (as applicable)
- Review of Subject Dosing Diary by Investigator and/or designee
- Assessment of AEs
- Assessment of concomitant medications
- Next visit scheduling

6.2.3 Day 7 Visit

Patiromer dose may be adjusted on Day 7 based on the potassium level measured locally according to the titration algorithm. A description of the patiromer dose titration algorithm is provided in Section 5.2.1.

The activities for Day 7 (± 3 days) are detailed below and in Appendix A:

- Subject's visit registration in IWRS
- Vital Signs (resting heart rate and sitting BP)
- 12-Lead ECG (Only if local K+ is > 6.0 mEq)
- Blood or serum potassium levels (measured locally) and serum potassium measured by central laboratory
- Serum chemistry (measured by central laboratory)
- Patiromer dose titration (if needed), dispensation, reconciliation, accountability, compliance, and subject retraining (as applicable)
- Review of Subject Dosing Diary by Investigator and/or designee
- Assessment of AEs
- Assessment of concomitant medications
- Next visit scheduling

6.2.4 Day 14 Visit

Patiromer dose may be adjusted at the Week 2 (Day 14) Visit based on the potassium level measured locally according to the titration algorithm. A description of the patiromer dose titration algorithm is provided in Section 5.2.1.

The activities for Day 14 (± 3 day) are detailed below and in Appendix A:

- Subject's visit registration in IWRS
- Physical examination
- Body weight and height
- Vital Signs (resting heart rate and sitting BP)
- 12-Lead ECG (Only if local K+ is > 6.0 mEq)
- Potassium levels (measured locally and by central laboratory).
- Other central laboratory tests (see Appendix B):
- Serum chemistry
- Plasma parathyroid hormone
- Serum fluoride
- Urinalysis (not required for anuric subjects, see section 7.2)
- Hematology (CBC)
- Patiromer dose titration (if needed), dispensation, reconciliation, accountability, compliance, and subject retraining (as applicable)
- Parent's or legally authorized representative's assessment of subject's (< 6 years of age) acceptance of patiromer
- Review of Subject Dosing Diary by Investigator and/or designee
- Assessment of AEs
- Assessment of concomitant medications
- Next visit scheduling

6.2.5 Week 3, Week 5, Week 7, Week 10, Week 14, Week 18, and Week 22 Visits

Patiromer dose may be adjusted at any scheduled visit based on the potassium level measured locally according to the titration algorithm. A description of the patiromer dose titration algorithm is provided in Section 5.2.1. Study visits at Week 3, Week 10 and Week 22 may be omitted under certain circumstances; refer to Section 3.2.3 for details. During the Long-Term Treatment Phase, up to 2 non-sequential study visits may be conducted remotely using the Sponsor approved Home Care vendor at certain investigational sites in certain countries; refer to Section 3.2.3 for details.

The activities for Week 3 (± 3 days) and Weeks 5, 7, 10, 14, 18, and 22 (± 7 days) are detailed below and in Appendix B:

- Subject's visit registration in IWRS
- Vital Signs (resting heart rate and sitting BP)
- 12-Lead ECG (Only if local K+ is > 6.0 mEq)

-
- Physical examination (Week 7 and Week 14 only); may be omitted for Home Care visit
- Body weight and height (Week 7 and Week 14 only); may be omitted for Home Care visit
- Potassium levels (measured locally and by central laboratory); the investigator will review local potassium results within 24 hours for any Home Care visit.
- Other central laboratory tests for Week 7 and Week 14 only (see Appendix B):
- Serum chemistry
- Serum fluoride
- Hematology (CBC)
- Patiromer dose titration (if needed), dispensation, reconciliation, accountability, compliance, and subject retraining (as applicable). For Home Care visits, the investigator will make decisions about patiromer dose titration within 24 hours after the visit; the subject or guardian will be contacted as soon as feasible if the investigator determines that a dose adjustment is required; any dose adjustment will take place at the next administered dose
- Assessment of AEs
- Assessment of concomitant medications
- Next visit scheduling

6.2.6 Week 26 Visit

The Week 26 Visit is the last visit of the Long-Term Treatment Phase. This visit is performed approximately 6 months after the Baseline Visit (Day 1) and the next day following administration of the last dose of patiromer.

The activities for Week 26 (± 7 days) are detailed below and Appendix B:

- Subject's visit registration in IWRS
- Physical examination
- Body weight and height
- Vital Signs (resting heart rate and sitting BP)
- 12-Lead ECG
- Potassium levels (measured locally and by central laboratory)
- Other central laboratory tests (see Appendix C):
- Serum chemistry
- Plasma parathyroid hormone
- Serum fluoride
- Urinalysis (not required for anuric subjects, see section 7.2)

- Hematology (CBC)

- Urine pregnancy test (female subjects of child-bearing potential only; measured locally and by central laboratory). In the event of a positive or equivocal urine pregnancy test result or if the subject is anuric, a serum Pregnancy test will be performed.
- Patiromer reconciliation, accountability and compliance
- Assessment of AEs
- Assessment of concomitant medications
- Next visit scheduling

6.3 Follow-up Period

Subjects who complete the Long-Term Treatment Phase will enter the 2-week Follow-up Period thereafter. Subjects who discontinue treatment with patiromer early during either the 14-day PD / Dose Finding Phase or Long-Term Treatment Phase enter directly into the Follow-up Period. The Follow-up Period consists of one visit (Follow-up Visit 1) at 1 week after the last patiromer treatment and one phone call (Follow-up Visit 2) at 2 weeks after the last patiromer treatment. Follow-up Visit 2 may be converted into an onsite visit at the investigator's discretion if potassium level from Follow-up Visit 1 is of concern.

6.3.1 Follow-up Visit 1 (F1)

Subjects must return for the F1 Visit 7 days (± 3 days) after stopping patiromer treatment (see Section 6.3 and Appendix B).

The following activities will be performed:

- Subject's visit registration in IWRS
- Vital Signs (resting heart rate and sitting BP)
- 12-Lead ECG (Only if local K+ is > 6.0 mEq)
- Potassium levels (measured locally and by central laboratory)
- Serum chemistry (see Appendix C)
- Assessment of AEs
- Assessment of concomitant medications
- Next phone call scheduling

6.3.2 Follow-up Visit 2 (F2)

Follow-up Visit 2 is a phone call to the subject's parent or legal guardian 14 days (± 3 days) after stopping patiromer treatment (see Section 6.3 and Appendix B). If subjects are requested to return for an onsite visit, the same activities will be performed as those listed in Section 6.3.1.

The following activities will be performed based on the phone call:

- Subject's visit registration in IWRS
- Assessment of AEs
- Assessment of concomitant medications

6.4 Early Termination Visit

Subjects who withdraw prematurely from the study before the Week 26 Visit will need to complete the ET Visit, which should be performed on the day of withdrawal or as soon as possible after the last dose of patiromer. Subjects who prematurely stop study drug should be encouraged to complete the Follow-up Period Visits (Section 6.3, Appendix A and Appendix B).

The following activities will be performed:

- Subject's visit registration in IWRS
- Physical examination
- Body weight and height
- Vital Signs (resting heart rate and sitting BP)
- 12-Lead ECG
- Potassium levels (measured locally and by central laboratory).
- Other central laboratory tests (see Appendix C):
- Serum chemistry
- Plasma parathyroid hormone
- Serum fluoride
- Urinalysis (not required for anuric subjects, see section 7.2)
- Hematology (CBC)
- Urine pregnancy test (women of child-bearing potential only; measured locally and by central laboratory). In the event of a positive or equivocal urine pregnancy test result or if the subject is anuric, a serum Pregnancy test will be performed
- Follow-up visit scheduling
- Patiromer reconciliation, accountability, compliance
- Assessment of AEs
- Assessment of concomitant medications

6.5 Other Visits

6.5.1 Safety Visit

Safety Visits are mandatory in certain situations. Mandatory Safety Visits are required within 7 days if subject meets any of the following criteria:

- Local potassium is > 6.0 mEq/L. If the patiromer dose is already at the maximum dose (or anticipated highest dose) for the age group, standard of care for hyperkalemia should be applied including RAASi dose decrease
- Any increase in patiromer dose that is initiated and the next scheduled study visit is > 1 week after the dose increase has been initiated
- Discontinuation per the Investigator's discretion

Note: During the 14-Day PD/Dose finding phase when local potassium measurements > 6.0 mEq/L, the Mandatory Safety Visit is not required if a standard study visit takes place within 3 days, however all listed MSV study procedures must be completed (i.e. ECG) at the standard study visit.

Treatment of these subjects with emergency care for hyperkalemia or prohibited standard of care medications (i.e., sodium polystyrene sulfonate or calcium polystyrene sulfonate) may result in the subject being removed from the study; see Section 5.6 for a complete list of prohibited medications. Investigator must contact the medical monitor to determine if the subject should continue in the study.

The following activities will occur during a Mandatory Safety Visit:

- Subject's visit registration in IWRS
- Vital Signs (resting heart rate and sitting BP)
- 12-Lead ECG if the current or most recent local potassium is > 6.0 mEq/L
- Potassium levels (measured locally and by central laboratory)
- Patiromer dose titration (if needed), dispensation, reconciliation, accountability, compliance, and subject retraining (as applicable)
- Assessment of AEs
- Assessment of concomitant medications
- Next visit scheduling

An unscheduled visit may occur at the discretion of the Investigator. At an unscheduled visit during any phase of the study, the following activities will be performed:

- Subject's visit registration in IWRS
- Assessment of AEs
- Assessment of concomitant medications

Other study procedures described in the protocol including the assessment of potassium levels (measured locally and by central laboratory) may be conducted at the discretion of the Investigator depending upon the reason for the visit.

7 ASSESSMENTS

7.1 Potassium

Eligible subjects must have K^+ levels of 5.1 – < 6.5 mEq/L determined by two blood or serum potassium measurements performed on separate days. A standard of care potassium value measured within 42 days to 2 days prior to Screening may be used for one of the potassium values to assess eligibility. Subject's eligibility will be assessed during a Screening Period with up to two visits (Screening Visit 1, Screening Visit 2).

The following scenarios are allowed for obtaining the two qualifying potassium values (5.1 to < 6.5 mEq/L):

- For subjects **with a recent standard of care potassium measurement**, the two qualifying potassium values will be the most recent standard of care potassium measurement obtained from 42 days to 2 days prior to Screening Visit 1 and the local potassium measurement at Screening Visit 1
- For subjects **without a recent qualifying standard of care potassium** measurement within 42 days to 2 days prior to Screening Visit 1, the first qualifying potassium values will be obtained at Screening Visit 1 and the second at Screening Visit 2, occurring 2 to 7 days after Screening Visit 1

Blood and/or serum potassium levels will be assessed at every study visit (with the exception of Follow-up Visit 2, which is a phone call) and measured both locally and by central laboratory. Serum samples will be used for central laboratory potassium measurements. For Follow-up Visit 2, if the subject is requested to return for an onsite visit, then blood/serum potassium levels will be assessed (see Section 6.3.2 for details).

7.1.1 Preventing, Identifying and Handling Hemolyzed Samples

Hemolysis of blood specimens may result in spuriously high potassium levels, leading to inappropriate up-titrating of the investigational product and causing difficulties in interpreting the efficacy analyses.

The Laboratory Manual provides detailed descriptions of the recommended phlebotomy, sample preparation and transportation procedures to minimize hemolysis.

Upon receipt of each blood sample for potassium analysis, the central laboratory will perform a semi-quantitative test to assess for evidence of hemolysis. Pre-defined criteria have been established for determining whether the test result is indicative of potential hemolysis. These criteria and the criteria for removing serum potassium value from the efficacy analyses on the basis of hemolysis are described in the Laboratory Manual. When a central laboratory sample has been identified as hemolyzed after it has been received and processed by the central laboratory, the blood draw will not be repeated by the site personnel. The statistical analysis plan (SAP) summarizes how the data analyses will account for the missing central laboratory potassium value. If the central laboratory blood sample has been identified as hemolyzed by the site personnel before it has been sent to the central laboratory, a repeat blood draw can be performed if the subject is still at the site.

When a blood sample, which is used by the site for titration and subject management, has hemolyzed (e.g., by visual inspection of the central laboratory serum sample), the site will need to repeat the potassium measurement from a separate blood draw in order to ensure accurate decision-making regarding patiromer titration.

7.1.2 Early Withdrawal from the Study due to Potassium Levels

Study withdrawal based on potassium level is at the discretion of the Investigator, except in the situations described in Section 6.5.1. The Investigator should perform a confirmatory local potassium level before initiating subject withdrawal. Aside from adjustment of diet or adjustment of concomitant medications (e.g., RAASi dose decrease or discontinuation in the Long-Term Treatment Phase), a potassium level that requires treatment with additional medications may be a reason for ET. If a subject is early terminated because of high or low potassium, the Investigator will provide the appropriate medical management for high or low potassium according to standard of care practices.

7.2 Laboratory Tests

AST, ALT and creatinine levels will be analyzed at the local laboratory at the Screening Visit(s) to assure eligibility for the study. Magnesium level will also be analyzed at the local laboratory at the Screening Visit(s). At other time points, the AST, ALT, magnesium and creatinine levels will be analyzed by the central laboratory as per Appendix A and Appendix B. Additional tests included in the chemistry panel (Appendix C) will be analyzed by the central laboratory at time points included in Appendix A and Appendix B. For subjects that have one dose of phosphate binder replaced by patiromer, calcium and/or phosphate levels may be tested by the central laboratory more frequently per Investigator's decision.

To qualify for study entry, the subject must have an eGFR < 90 mL/min/1.73m^2 at screening based on local measurements. Either the Original or Bedside Schwartz formula should be used to calculate eGFR based upon the current serum creatinine assay methodology being used at the investigative site's local clinical laboratory.

- The Bedside Schwartz formula [eGFR = 0.413 × [height (cm)/serum creatinine (mg/dL)] (Schwartz, 2009) requires enzymatic creatinine assay, which may not be available at all institutions. In cases where the study site's local laboratory uses the Jaffe creatinine assay that is isotope dilution mass spectrometry (IDMS) traceable, then the Bedside Schwartz formula should be used to calculate eGFR

- In clinical laboratories that use the Jaffe method for creatinine determination that is not isotope dilution mass spectrometry (IDMS) traceable, eGFR should be calculated using the Original Schwartz formula [eGFR = k × [height (cm)/serum creatinine (mg/dL), where the value for k is 0.45 for term infants through the first year of life, 0.55 for children and adolescent girls and 0.7 for adolescent boys] (Schwartz, 2009)

Hematology (CBC including WBC, RBC, hemoglobin, hematocrit, and platelet count) will be analyzed by the local laboratory at the Screening Visit(s) to assure eligibility for the study. At other

time points, the hematology panel (Appendix C) will be assessed by central laboratory as per Appendix A and Appendix B.

For female subjects of child bearing potential only, a urine pregnancy test will be assessed locally and a serum pregnancy test will be performed by the central laboratory. For anuric female subjects of child bearing potential, a serum pregnancy test will be assessed locally and by the central laboratory. Anuric female subjects of child bearing potential cannot be enrolled into the study until a local negative serum pregnancy test is demonstrated.

Urinalysis (see Appendix C) will be assessed by central laboratory. Urinalysis will not be required for anuric subjects.

7.3 Vital Signs

7.3.1 Heart Rate

In children over 2 years of age, heart rate can accurately be assessed by measuring the pulse radially in most children. In the event peripheral pulses are difficult to palpate, heart rate may be assessed by auscultation of the apical pulse for one full minute. The apical pulse is assessed over the point of maximum impulse (PMI) on the child's chest. In children up to 7 years old, the PMI is usually found at the 4th rib interspace medial to the nipple (the midclavicular line). After Age 7 - 8, the PMI is found between the 5th and 6th interspace, as it is in the adult.

Heart rate should be measured prior to BP measurement, and should be measured for a full 60 seconds. Heart rate data for each visit should be recorded in the respective eCRF.

7.3.2 Blood Pressure

When taking BP measurements, Investigators shall follow the following recommendations:

- Throughout the study, BP measurements should be performed using the same device for each subject.
- Correct measurement requires a cuff that is appropriate to the size of the child's upper arm (US Department of Health and Human Services, 2005)
- Measurements should be taken in a quiet place. The child whose BP is to be measured should have avoided stimulant drugs or foods and have been sitting quietly for 5 minutes
- Tight-fitting clothing should be removed from the arm to be measured. The same arm should be used for all BP measurements
- During the measurement, the subject should be seated with feet flat on the floor, back supported and arm rested on a table so that the cuff is at the subject's heart level. If this is not possible, the same positioning of the subject should be maintained for BP measurement at each visit

Subject should remain still and should not talk during the measurement. BP data for each visit should be recorded in the respective eCRF.

7.4 Physical Examination

Physical examination should be performed as indicated in the Schedule of Events (see Appendix A and Appendix B). The following body systems are to be examined:

- Cardiovascular
- Lungs and chest, including respirations
- Head and neck
- Abdomen
- Musculoskeletal
- Skin
- Neurological

Any new clinically significant physical examination abnormality identified during the study should be reported as an AE.

7.5 ECG Assessment

The baseline 12-lead ECG may be performed on either Screening Visit 1 or Screening Visit 2; the end of study ECG will be performed at the Week 26 Visit or ET visit.

If the Investigator is concerned regarding any potassium value, a re-test of potassium level and/or ECG evaluation for electrophysiological consequences can be initiated by the Investigator at their discretion. An ECG is required when the local K^+ is > 6.0 mEq/L and must be followed by a Mandatory Safety Visit (See Section 6.5.1)

If a potassium-related ECG change is observed, the Investigator should apply the appropriate standard of care to stabilize the myocardium, which may include any or all of the following depending on the subject's clinical situation: intravenous calcium, intravenous insulin and glucose, inhaled $beta_2$ agonists. In all cases, the ECG should be repeated within 2 to 3 minutes following any of the above interventions, and the subject should be assessed for referral to an emergency care facility. Any subject with a potassium-related ECG change must be withdrawn early and once stable, should return for the ET Visit (see Section 6.4).

7.6 Patiromer Palatability

The 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 using a 5-point facial hedonic scale for taste and overall liking. Patiromer should be mixed with water on Day 1 for the palatability assessment. Parental or authorized legal representative response on a 5-point agreement/disagreement scale to a statement of the subject's (< 6 years of age) acceptance of patiromer will be assessed on Day 14.

7.7 Fluoride

Serum fluoride levels will be assessed as a part of the safety analysis and will be performed at Screening Visit 1 or Screening Visit 2, in addition to Week 2 (Day 14), Week 7, Week 14, Week 26 and ET Visits.

Systemic fluoride supplementation, other than local municipal water supply, is not recommended and careful parental or legal guardian supervision of fluoride containing toothpaste and or dental rinse (if applicable) use by younger subjects (< 6 years of age) is advised to prevent accidental ingestion.

7.8 Diet

Subjects will be instructed to continue their usual diet during the study.

8 ADVERSE EVENT REPORTING

8.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment (Clinical Safety Data Management, 1995). An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes: 1) any new medical condition, sign or symptom, clinically significant physical examination abnormality or newly diagnosed event that occurs during the AE reporting period (see Section 8.2.1), including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period; 2) a preexisting condition that has worsened in severity or frequency or changed in character after the legally authorized representative signs the informed consent and subject signs the assent (if required) during the AE reporting period; and 3) complications that occur as a result of protocol-mandated interventions. An AE can arise from any use of the investigational drug (e.g., off-label use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. It also includes any side effects, injury, toxicity or sensitivity reactions that may be experienced by a subject in this clinical trial.

Out of range laboratory results, ECGs, vital signs and other safety assessments will be considered AEs if they meet at least one of the following criteria:

- Associated with symptoms or lead to a diagnosis (in such case the symptom or diagnosis should be recorded as an AE)
- Lead to discontinuation of patiromer
- Required treatment or subject referral for further testing outside the protocol (repeat testing or titration are within protocol procedures)
- The Investigator or Relypsa considered the abnormality as clinically significant in its own right (e.g., asymptomatic creatinine kinase > 5000 IU/L)

For the purposes of this protocol, events that are not considered AEs include:

- Anticipated fluctuating signs or symptoms of a pre-existing medical condition (e.g., tremor in a subject with Parkinson's disease; migraine episodes) that have not worsened in severity or frequency or changed in character during the AE reporting period
- Surgeries or medical procedures are not AEs, however, the medical condition (new or worsened) that led to the surgery or medical procedure is the reported AE (e.g., for appendicitis resulting in appendectomy, appendicitis would be reported as the AE)
- Overdose without clinical signs or symptoms
- Pregnancy (see Section 8.4 for reporting obligations)

8.1.1 Definition of Serious Adverse Event

An SAE is an AE that meets one or more of the following criteria:

- **Results in death.**
- **Life threatening experience** defined as any AE that in the view of the Investigator or Relypsa, places the subject at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**, with the exception of:

- Visits to the emergency room or hospital department that do not result in an in-patient admission
- Elective surgery for a pre-existing condition that has not worsened
- Routine health assessments requiring admission
- Social admission (lack of housing, family circumstances, etc.)

- **Results in persistent or significant disability/incapacity** (i.e.: a substantial disruption of the ability to conduct normal life functions / normal activities of daily living)
- Is a **congenital anomaly or birth defect** in an offspring of a female subject taking patiromer or a congenital anomaly or birth defect in the female partner of a male subject taking patiromer during the conduct of the clinical study
- Is an **important medical event** that may not be immediately life-threatening or result in death or hospitalization but based upon medical judgment, jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes above (e.g., blood dyscrasias; convulsions)

Either the Investigator or Relypsa can determine that an AE meets the definition of seriousness. If either believes that the event is serious, the event must be considered serious and evaluated by Relypsa for expedited reporting.

8.2 Procedures for Eliciting, Recording and Reporting Adverse Events

8.2.1 Adverse Event Reporting Period

AEs, including SAEs, will be collected throughout the study period, beginning from the time the ICF is signed until the subject's last study visit (normally the last follow-up visit). Any AE or SAE will be followed until it resolves or becomes stable. The Investigator must report any AEs that occur after the protocol specified reporting period if according to the Investigator's assessment there was a reasonable possibility that the AE was related to patiromer or any study procedures.

8.2.2 Eliciting Adverse Events

Information on AEs and SAEs will be elicited at each AE assessment time point specified in the Schedule of Events by asking an open-ended question such as: "Since you were last asked, have you felt unwell or different from usual in any way?" The subject or the subject's legally authorized representative may report AEs spontaneously at any time.

8.2.3 Assessing Adverse Events

The Investigator should follow the guidelines for rating severity of AEs:

Mild: No disruption to normal activities. Awareness of signs or symptoms, but easily tolerated; symptoms are transient and would not require medication or medical evaluation.

Moderate: Some disruption to normal activities. May lead to discomfort, treatment may be required.

Severe:Significant disruption to normal activities. May be incapacitating; may require medical evaluation and/or treatment.

The term "severe" is often used to describe the intensity of a specific event; the event itself, however, may be of relatively minor medical significance, such as severe headache. Severity of the event is not the same as seriousness, which is a regulatory definition. Regardless of the severity, an AE is serious if it meets any of the seriousness criteria (see Section 8.1.1).

To allow for an objective comparison of the severity of the drug-related gastrointestinal (GI) AEs, severity of specific GI AEs (i.e., constipation, diarrhea, abdominal discomfort, nausea, flatulence and vomiting) will be evaluated by using the descriptors listed in

Table 5, which are based on the DAIDS Table for Grading the Severity of Adult and Pediatric AE (Division of AIDS National Institute of Allergy and Infectious Diseases, Version 2.0, 2014).

The DAIDS grading system does not provide any grading for flatulence. In children, gas-related symptoms are reported more frequently as bloating, distension or abdominal discomfort. Therefore, bloating or distension are evaluated by the Investigator based on the severity according to the descriptions specified in Table 5. The DAIDS grading system does not include an exact term for abdominal discomfort; the term "pain" is modified to describe abdominal discomfort. For these GI events, the Investigator should assess severity according to the descriptions specified in, which are

based on the DAIDS grading system but have been modified to account for the study population and drug safety profile. AEs that are life-threatening (DAIDS Grade 4) or resulting in death (DAIDS Grade 5) meet reporting criteria for SAEs.

Table 5: Categories of Severity for Specified GI AEs

PARAMETER	MILD[a]	MODERATE[b]	SEVERE[c]
Abdominal discomfort or pain	Pain or discomfort causing no or minimal interference with usual social & functional activities	Pain or discomfort causing greater than minimal interference with usual social & functional activities	Pain or discomfort causing inability to perform usual social & functional activities Or Disabling pain or discomfort causing inability to perform basic self-care functions OR Hospitalization indicated
Bloating or Distension **Report only one**	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social and functional activities
Constipation[d]	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated Or Life-threatening consequences (e.g., obstruction)
Diarrhea **≥ 1 year of age**	Transient or intermittent episodes of unformed stools OR Increase of ≤ three stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated Or Life-threatening consequences (e.g., hypotensive shock)
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids) Or Life-threatening consequences (e.g., hypotensive shock)

[a] Based on DAIDS Grade 1 as described in the table.

[b] Based on DAIDS Grade 2 as described in the table.

[c] Based on DAIDS Grade 3 and 4 but does not include events resulting in death (DAIDS Grade 5).

[d] DAIDS grading system does not include a description for Grade 1 constipation; therefore, Grade 1 constipation from CTCAE version 4.03 criteria is used.

Table 5: Categories of Severity for Specified GI AEs (Cont'd)

PARAMETER	MILD[a]	MODERATE[b]	SEVERE[c]
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids) Or Life-threatening consequences (e.g., hypovolemic shock)

[a] Based on DAIDS Grade 1 as described in the table.

[b] Based on DAIDS Grade 2 as described in the table.

[c] Based on DAIDS Grade 3 and 4 but does not include events resulting in death (DAIDS Grade 5).

[d] DAIDS grading system does not include a description for Grade 1 constipation; therefore, Grade 1 constipation from CTCAE version 4.03 criteria is used.

8.2.4 Causality Assessments

The Investigator will provide a causality assessment for all AEs using his/her best clinical judgment based upon the available medical information of the event that is being reported. The causality assessment will be re-assessed as new medical information becomes available. If the Investigator's causality assessment is not reported it will be considered as "related" until it is received. The Investigator and Relypsa will each assess relatedness of the AE to the investigational drug, patiromer, using the following definitions:

Not Related: There is no reasonable possibility that patiromer caused or contributed to the AE.

- The event is related to an etiology other than the investigational drug (the alternative etiology, such as underlying disease, study or non-study procedures, concomitant medications, or the subject's clinical state)
- The time of the occurrence of the AE is not reasonably related to the administration of the study drug

Related: There is a reasonable possibility that patiromer caused or contributed to the AE.

- There is a compatible temporal association between the event and the administration of investigational drug
- There is a biologically plausible mechanism for the study treatment to cause or contribute to the AE
- The event improves or diminishes upon withdrawal of the study drug without the initiation of any specific treatments for the event (dechallenge), and/or the event recurs or worsens with the rechallenge of the study therapy
- The event cannot be reasonably attributed to concurrent or underlying illness, other drugs or procedures

For causality assessment purposes "reasonable possibility" is defined as based on the Investigator's medical judgment of the available information there are facts or arguments to suggest a positive causal relationship.

8.2.5 Recording Adverse Events

All AEs and SAEs, whether spontaneously reported by the subject, subject's legally authorized representatives or elicited or noted by study staff, will be recorded in the subject's medical record and on the appropriate AE CRF or eCRF page. In addition, the SAE Report Form must be completed for each SAE.

AEs related to an etiology other than the investigational drug (the alternative etiology, such as underlying disease, study or non-study procedures, concomitant medications, or the subject's clinical state, must be documented in the study subject's medical record and provided in the AE eCRF and, if applicable, the SAE report).

All AEs should be recorded using the words of the subject or subject's legally authorized representatives (verbatim term) to describe the AE whenever possible. However, if the verbatim term is vague or ambiguous (e.g., cramps), the study staff should try to obtain clarification by asking a follow-up question (e.g., what kind of cramps?) and record the words the subject used to clarify the event (e.g., menstrual cramps, calf muscle cramps). Additionally, if the subject reports a group of symptoms that the Investigator uses to make a unifying diagnosis, the diagnosis will be recorded instead of the symptoms (e.g., rhinopharyngitis instead of runny nose, cough, sore throat and sneezing). If a diagnosis is unknown, signs and symptoms need to be recorded separately until a diagnosis is determined, at which time the diagnosis will be reported in lieu of the symptoms.

The following information will be captured for each AE: date of onset and resolution, outcome, severity (as defined in Section 8.2.3), seriousness criteria, Investigator's causality assessment for the relatedness of the AE to the investigational drug, action taken with the investigational drug and treatments administered. Any treatment administered as a result of an AE should be recorded on the Concomitant Medication CRF and/or Surgical and Medical Procedure CRF as applicable.

8.3 Serious Adverse Events Reporting

8.3.1 SAE Notification

The Investigator has the obligation to report each SAE to Relypsa or designee within 24 hours of knowledge of the occurrence. Follow-up reports must be submitted in the same time as the initial report (within 24 hours) as additional information becomes available. If the Investigator learns of any SAE that occurred after the Follow-up Period for which there is a reasonable possibility of relatedness to the investigational drug, that event and subsequent follow-up information must be reported within 24 hours.

Cause of death is required whenever known. If an autopsy was performed, an autopsy report should be provided. If an autopsy was not conducted, a Death Certificate should be provided if obtainable. Death should be reported as an outcome and not as an event.

SAEs must be reported by entering the SAE information into the AE CRF in the EDC system. If the event meets seriousness criteria, SAE reporting via the paper SAE Report Form will be required. The Investigator must complete a paper copy of SAE report form, scan and e-mail or fax it to the contact provided in the SAE and Pregnancy Reporting Guidelines.

The SAE information must be entered onto the SAE CRF as soon as the EDC system becomes accessible, and before additional new information is entered. All SAEs should be followed until they are resolved, stabilized or otherwise justified by the Investigator in agreement with Relypsa and all relevant information is compiled.

The SAE Form will be completed with the following information at a minimum:

- Trial number/ trial center
- Name of reporter/Investigator
- Subject identification number
- SAE term
- Date of onset
- Date of outcome or resolution (when medically applicable)
- Outcome
- Criteria of seriousness
- Severity of the event
- Relatedness to patiromer

Additional information must be provided when available, and any relevant records (hospital Discharge Summary, Autopsy Report/Death Certificate, diagnostic study reports, etc.).

8.3.2 SAE Expedited Reporting

Relypsa will notify all Investigators of all SAEs requiring expedited reporting to Regulatory Authorities.

The Investigator is responsible for notifying the IRB in accordance with local regulations of all SAEs that occur. The Investigator must review and file the safety report with the Investigator's Brochure.

Relypsa is responsible for notifying the applicable Health Authorities of SAEs in accordance with applicable laws and regulations.

Suspected Unexpected Serious Adverse Reactions (SUSAR)

Relypsa, or designee, will be responsible for submitting expedited safety reports to the Regulatory Authorities, as required by the current local regulations. Relypsa or designee will be responsible for reporting SUSARs to the Regulatory Authorities concerned and the IRBs/IECs as soon as possible but within a maximum of 15 calendar days of Relypsa's first knowledge of the event. All

SUSARs that are fatal or life-threatening will be reported to the Regulatory Authorities concerned and the IRBs/IECs within 7 calendar days of the first knowledge of the event; relevant follow-up information regarding fatal or life-threatening SUSARs will be subsequently communicated within an additional 8 days.

8.4 Procedures for Reporting Pregnancy Exposure and Birth Events

Should a female subject become pregnant or be suspected of being pregnant while participating in this study, the investigational product will be permanently discontinued, and the event must be reported to Relypsa upon receipt of information by the study staff. Pregnancies must be reported throughout the conduct of the study including two weeks following the last dose of study drug received. Pregnancy reporting includes exposure of the female partner of a male subject. While pregnancy is not considered an SAE, it must be reported to Relypsa within 24 hours of becoming aware on the Pregnancy Monitoring Form. Pregnancy complications are reported as AEs or SAEs (if applicable). Any pregnancy will be followed through delivery for the observation of any SAEs. Fatalities, elective or spontaneous abortions, congenital abnormalities/birth defects and AEs/SAEs occurring in the newborn must be reported as SAEs. Newborns potentially exposed to study drug via maternal or paternal sources who experience a SAE before, during, or after delivery (including lactation by the maternal subject) will be followed until resolution of the event or for a minimum of 12 weeks.

8.5 Study Management Committee

The SMC includes Sponsor representatives and the lead study investigator. The SMC will review data from the study on an ongoing basis. Within pre-specified guidelines, the SMC will have the authority to make modifications to the study dose and titration plan between meetings of the independent DSMC. For instance, the SMC could extend the number of subjects being treated in an age/dose cohort, even if no specific safety issues were encountered, to allow collection of additional data. The prespecified guidelines will be detailed in the DSMC Charter and SMC Plan.

8.6 Data and Safety Monitoring Committee

Prior to initiation of the study, an independent DSMC will be established. The DSMC will act in an advisory capacity to Relypsa to monitor the safety of patiromer in subjects who participate in the study. In general, the DSMC responsibilities will include:

- Protect the safety of the study participants in accordance with the study protocol and DSMC Charter
- Review and evaluate all relevant information that may have an impact on the safety of the study participants or the ethics of the study
- Assess risks and benefits to study participants
- Make recommendations to Relypsa concerning continuation, termination or other modifications of the study
- Review safety, dosing and pharmacodynamic data throughout the study

Based on this review, the DSMC will provide a recommendation to evaluate another starting dose in an age group or to evaluate the current dose in additional subjects in that age group. Dose escalation and/or stopping criteria are pre-identified based on pre-specified safety criteria or on the lack of sufficient response as described below.

The DSMC charter will provide additional details concerning the review and recommendation process.

8.6.1 Dose Escalation

Evaluation of Starting Dose Levels:

During the 14-day PD / Dose Finding Phase the Investigator will be allowed to up-titrate the patiromer dose according to a protocol-specified algorithm. A description of the patiromer dose titration algorithm is provided in Section 5.2.1.

After three subjects complete their 14-Day PD / Dose Finding Phase, PD, dosing and safety data will be provided to the DSMC. The DSMC will evaluate these data, as well as the number of subjects requiring dose titration. Based on its review, the DSMC will determine if the starting dose for subjects under review was acceptable for a recommended starting dose, in which case nine additional subjects (or fewer if more than three subjects were initially enrolled) in the same age group will be enrolled at the same starting dose. If the DSMC determines that the starting dose and/or titration pattern did not result in an acceptable PD response, but the safety was acceptable, the DSMC will provide a recommendation to evaluate the next higher starting dose in the age group.

Subject screening will pause periodically throughout the study to allow for preparation of data and DSMC review and provision of recommendations. Any subjects who are in the Screening Period when the pause is announced may be enrolled provided they meet all eligibility criteria. Details regarding DSMC review criteria are described in the DSMC charter.

The DSMC will evaluate the following subject-level parameters in assessing a patiromer starting dose level:

- Achieving a target serum potassium range of 3.8 – 5.0 mEq/L
- Clinically relevant decrease in serum potassium
- Number of dose up-titrations above the starting dose
- Patient safety information

The DSMC will consider the baseline and change in serum potassium level in determining if an observed decrease in serum potassium is clinically relevant for subjects that do not achieve the target potassium range. In addition, the DSMC will consider the proportion of subjects that had up-titrations of patiromer to ensure a recommended starting dose is close to the effective dose (e.g., up-titrations required in all three subjects may suggest the starting dose was too low).

Section 5.2 describes the planned starting doses in all age groups. The DSMC will recommend the starting doses for the 6 – <12 year old age group upon evaluation of PD and safety data for the

entire 12 – <18 year old age group through Day 14. Similarly, such an evaluation also will occur when the entire 6 – <12 year old group completes Day 14 in order to recommend starting doses for the 2 – <6 year old group.

8.6.2 Stopping Criteria

Safety Criteria:

The safety profile of patiromer in children > 2 years of age is expected to be similar to the safety profile of patiromer observed in adults (see Section 1.2).

In addition to the AEs mentioned in

Table 5 (see Section8.2.3) that will be evaluated by the Investigator based on the descriptions in

Table 5 (see Section8.2.3), the DSMC will review all other AEs (including SAEs) using standard severity descriptors (mild, moderate and severe) included in the protocol. The DSMC will also review all central laboratory data, including occurrences of serum magnesium and potassium below the lower limit of normal as provided in the laboratory reports (see Section 8.6).

Deaths that are assessed as due to hypokalemia will be assessed as related to the investigational drug. Deaths that are assessed as due to hyperkalemia will be assessed as due to failure of the investigational drug.

Study or Dose Level Stopping Criteria:

- If two subjects experience the same severe GI AEs that in the opinion of the Investigator(s) and SMC **are related to patiromer**, the DSMC will be consulted to review the available safety data and either provide approval to continue dosing for all subjects or make recommendations regarding modification of starting dose and/or titration algorithms within an age group and sequentially in younger age groups by dose category
- If two subjects experience medically similar unexpected SAEs that in the opinion of the Investigator and SMC **are related to patiromer** the DSMC will be consulted to review the available safety data and either provide approval to continue dosing for all subjects or make recommendations regarding modification of starting dose and/or titration algorithms within an age group and sequentially in younger age groups by dose category
- If one subject experiences an unexpected SAE that is confirmed **to be related to patiromer**, no additional subjects in the same age cohort will be started on or up-titrated to the dose level at which the SUSAR occurred

For individual subjects experiencing any unexpected drug-related SAE or AE leading to withdrawal, the SMC will review the event and the DSMC will be notified at an ad hoc basis.

8.6.3 Frequency of DSMC Meetings

14-Day PD / Dose Finding Phase

The DSMC will meet after all three subjects in each age and dose cohort complete their 14-day PD / Dose Finding Phase to review their safety, dosing and pharmacodynamic data as described in

Section 8.6. An additional DSMC meeting will occur after the dose expansion group (n = 9) provide sufficient information from their 14-day PD / Dose Finding Phase. If a subject withdraws from the study within the 14-Day PD / Dose Finding Phase, the SMC will determine if sufficient information is provided for DSMC review. If insufficient information is provided, the DSMC meeting may be delayed.

Long-Term Treatment Phase

The DSMC will meet at regular intervals to conduct ongoing review of PD, dosing and safety data throughout the Long-Term Treatment Phase to monitor safety and evaluate the effectiveness of patiromer dose titration algorithms. The DSMC may make recommendations to modify the patiromer dose titration algorithms based upon their review. Additional details are provided in the DSMC Charter.

Ongoing DSMC Review

During the study, ad-hoc DSMC meetings may be requested by either the DSMC or SMC to review relevant information that may have an impact on patiromer dosing or the safety of the participants in the study.

9 DATA ANALYSIS / STATISTICAL METHODS

This section briefly describes the planned statistical methods for this study. A SAP will describe the methods in detail. If there is a difference between the language of this protocol and the language of the SAP, the SAP will take precedence over the protocol.

9.1 Randomization

No randomization is applied in this study.

9.2 General Considerations

Tables and listings will present results by age cohort and starting dose and will include demography, subject disposition, baseline disease characteristics and other medical history, and concomitant medications. Efficacy variables and analyses are discussed in Section 9.4. Safety variables and analyses are discussed in Section 9.5.

All analyses of potassium levels will use central laboratory values. The potassium values obtained locally and used to manage subjects' dose levels at study sites, may also be used in estimating missing central laboratory values.

The efficacy and safety populations will include all subjects who have taken at least one dose of patiromer. 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 statistics and will be included in listings only.

9.3 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%.

9.4 Efficacy Analysis

9.4.1 Primary Efficacy Variable

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 central laboratory serum potassium value prior to first dose of patiromer. Descriptive statistics include mean, standard deviation, and 95% confidence intervals.

9.4.2 Secondary Efficacy Variables

- 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.

9.4.3 Subgroups of Interest

The following baseline variables will be used to define subgroups of interest: gender, race and age groups. Additional subgroups of interest that may be examined will be included in the SAP.

9.5 Safety Analysis

Safety variables will include:

- All AEs
- SAEs
- Clinical laboratory test results
- Vital signs

- ECG
- Deaths
- Reasons for dosing interruption or discontinuation
- 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

The analysis of treatment-emergent AEs will include all events with onset or worsening on or after the date of first dose of patiromer.

Complete details of the safety analyses will be presented in the SAP.

9.6 Additional Analyses

In children ≥ 6 years old, if patiromer is administered onsite, patiromer palatability assessments (taste and overall liking) will be performed at Day 1, using a visual analog scale and will be summarized using descriptive statistics. For children < 6 years old parental or authorized legal representative assessment of the subject's acceptance of patiromer will be performed on Day 14 and will be summarized using descriptive statistics. Additional analyses that may be examined will be included in the SAP.

9.7 Handling of Missing Data

Detailed procedures for managing missing data in all analyses will be provided in the SAP.

10 DATA HANDLING AND RECORDKEEPING

10.1 Case Report Forms / Electronic Data Record

An eCRF is designed to record all of the protocol-required information to be reported to Relypsa on each trial subject. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported on subjects' eCRFs. Data reported on the eCRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. An explanation should be given for all missing data.

All eCRF data and query resolutions must be completed only by the clinical trial personnel designated by the Investigator. All site staff will have proper training prior to accessing the EDC system.

Any change or correction to an eCRF will be tracked via an audit trail within the EDC system. The audit trail will contain the original data value, new data value, date changed, the user who made the change, and the reason(s) for the change.

CRFs should be completed in a timely manner to support the study timeline (i.e., the site should not wait for a monitoring visit before entering data into the eCRF).

Data from the eCRFs and queries will be tracked and entered into a 21 CFR Part 11 compliant clinical database. The database system will be a secured, password-protected system with full audit trail utility.

Subject data will be reviewed via programmed quality checks and manually via data listings review by Relypsa and its designee. Data that appear inconsistent, incomplete, or inaccurate will be queried for site clarification. Data corrections will be updated to the database and tracked in the audit trail. AEs and concomitant medications will be coded using industry standard dictionaries (e.g., Medical Dictionary for Regulatory Activities [MedDRA] and World Health Organization [WHO] Drug dictionary).

The Investigator is responsible for reviewing, verifying, and approving all subject data (i.e., eCRFs and resolved queries).

10.2 Record Retention

The Investigator must maintain adequate records for the study including completed CRFs, medical records, laboratory reports, signed ICFs, drug disposition records, adverse experience reports, information regarding subjects who discontinued, all correspondence with the IRB/IEC and Relypsa, and other pertinent data.

The Investigator is to retain all records until notified by Relypsa. The Investigator will notify Relypsa in writing of the relocation of any study records away from the research facility after study closure. The Investigator must contact Relypsa in writing prior to the destruction of any study records, or in the event of loss of any study records.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The integrity and quality of subject data will be ensured by providing training and process instructions for the completion of the eCRFs, performing quality control checks, conducting ongoing clinical data review (including medical and safety reviews), and performing source data verification and data reconciliation.

Relypsa employees or designee will conduct site monitoring visits at regular intervals in accordance with FDA and International Conference on Harmonisation (ICH) guidelines. The Investigator will permit Relypsa or designee monitors to review and inspect facilities, and all records relevant to this study.

The Investigator will also permit Relypsa or designee auditors, the IRB/IEC, FDA or other Regulatory Authority inspectors to review and inspect facilities, procedures, and all records relevant to this study. These records include, but are not limited to: subject signed ICFs, source

documentation, regulatory and essential documents, CRFs, and drug accountability records. If the FDA or other regulatory agencies should schedule an inspection, the Investigator should notify Relypsa immediately.

The following steps will be taken to ensure that the trial is conducted by the investigational site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or Investigator site initiation
- Routine site monitoring
- Documented protocol and GCP training
- eCRF and query review against source documents
- Collection of local laboratory normal ranges

12 ETHICS

The study will be conducted in accordance with US FDA regulations, the ICH E6 guidelines for GCP, the Declaration of Helsinki, and IRB or IEC requirements. The study will also be conducted in accordance with the European Union Clinical Trials Directive 2001/20/EC (EUCTD) for sites in the EU and all other applicable local and national laws and regulations governing the conduct of human clinical studies.

12.1 Institutional Review Board / Independent Ethics Committee

All Investigators participating in this study must be governed under an appropriate IRB or IEC. The applicable IRB or IEC should review and approve this protocol, the ICF, the assent (if required), the Investigator's Brochure and any information to be given to the subject before a site can begin conducting any study-related activities. A copy of the IRB/IEC approval letter for the protocol, the ICF and the assent (if required) must be provided to Relypsa prior to investigational product shipment. The IRB/EC must approve any subject recruitment materials before the material is used for subject recruitment.

Subsequently, the Investigator is responsible for obtaining re-approval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the Investigator's annual report and other required reports to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to Relypsa. The Investigator must also inform the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, expedited reports of SAEs submitted to regulatory authorities, and other significant safety concerns according to the IRB/IEC policy. Written documentation of IRB approval of protocol amendments must be received before the amendment is implemented. After completion or termination of the study, Investigators will notify their IRB/IECs. The Investigator will comply with all IRB/IEC policies throughout the duration of the study.

12.2 Ethical Conduct of the Trial

The Investigator is responsible for assuring that the study is conducted in accordance with current local and national regulations, ICH GCP guidelines, and other applicable requirements governing the conduct of human clinical trials.

The Investigator will not deviate from the protocol without prior written approval from Relypsa, except in medical emergencies. In the event of a medical emergency, the Investigator must notify the Medical Monitor as soon as possible. Any other change to the protocol must be implemented as an amendment to the protocol and must be approved by the IRB/IEC prior to implementation.

The Investigator must inform the governing IRB/IEC of all protocol changes in accordance with the IRB/IEC's established procedure. No deviation from the protocol of any type will be permitted without complying with the established IRB/IEC procedures.

If an Investigator chooses to advertise for subjects, whether in professional or consumer publications, radio, or television, all advertising must be approved by Relypsa and the IRB/IEC prior to initiation.

Financing and insurance are covered in the Clinical Trial Agreement and Clinical Trial Insurance Policy.

12.3 Subject's Information and Informed Consent/Assent

Individual subject's medical information obtained as a result of this study is considered confidential and disclosure to unauthorized parties is prohibited. Subject's confidentiality will be assured by utilizing subject identification code numbers and/or initials, instead of names. If results of this study are reported in medical journals or at meetings, the subject's identity will not be disclosed.

With the legally authorized representative's authorization, medical information may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare.

Subjects under the age of 18 years (or 16 years, depending on the region) will provide written assent (if required), and his/her legally authorized representative (parent or legal representative) will provide written informed consent for such subjects.

In compliance with GCP guidelines, all subjects and legally authorized representatives will be informed of the purpose of the research, the possible risks, and their right to withdraw at any time from the study without prejudice and without jeopardy to their future medical care at the center. Each subject's legally authorized representative and subject must agree to cooperate in all aspects of the study and must give informed written acknowledgment (signed ICF) and assent (if required) to the Investigator prior to participation in the study. If the ICF and assent are revised during the study, active subject's legally authorized representatives and subject (if required) must sign the new version in order to continue participating in the study. For any updated or revised ICF, the subject record should state that written informed consent and assent (if required) was obtained for the updated/revised consent and assent (if required) form for continued participation in the trial. The ICF should be revised whenever there are changes to procedures in the amended protocol associated

with procedures in the ICF or when new information becomes available that may affect the willingness of the subject to participate. Every legally authorized representative will be given a copy of each version of the form that he/she signs before and during the study. In the United States, each ICF may also include authorization allowing the institution, Investigator and Relypsa to use and disclose personal health information in compliance with the Health Insurance Portability and Accountability Act of 1996 Health Information Portability and Accountability Act (HIPAA).

No subject is to participate in study activities until informed consent and assent (if required) has been obtained. Documentation of the informed consent and assent (if required) process and subject information discussion must appear in the subject's medical record, and include a statement that informed consent and assent (if required) was obtained prior to participation in the study. Signed acknowledgments (ICFs and assent forms) must remain in the subjects' files and be available for verification by monitors, auditors, and/or regulatory agency inspectors at any time. The final IRB/IEC-approved ICF and assent (if required) must be provided to Relypsa for regulatory purposes.

13 RELYPSA DISCONTINUATION CRITERIA

Discontinuation criteria for individual subjects and the study are included in the DSMC Charter. In addition, a variety of reasons may lead either Relypsa or a regulatory agency to terminate the study early.

14 PUBLICATION OF TRIAL RESULTS

The Clinical Trial Agreement describes Relypsa's publication terms.

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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	SV1	SV2/D1 (2 to 7 days after SV1)	D3[a] (± 1d)	D7 (± 3d)	D14 (± 3d)		
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	SV1	SV2/D1 (2 to 7 days after SV1)	D3[a] (± 1d)	D7 (± 3d)	D14 (± 3d)		
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	W3[i] ± 3d	W5 ± 7d	W7 ± 7d	W10[i] ± 7d	W14 ± 7d	W18 ± 7d	W22[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

[a] 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)

[b] Or any unscheduled visit

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

[d] 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.

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

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

[g] 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).

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

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

[j] 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)

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

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

Appendix C: List of Central Laboratory Assays

Serum chemistry panel:	**Hematology (CBC):**
Alanine aminotransferase (ALT)	White blood cell count (WBC)
Albumin	Red blood cell count (RBC)
Alkaline phosphatase	Hemoglobin
Aspartate aminotransferase (AST)	Hematocrit (Packed Cell Volume)
Bicarbonate	Mean cell volume (MCV)
Blood Urea Nitrogen (BUN)	Mean cell hemoglobin (MCH)
Calcium	Mean cell hemoglobin concentration (MCHC)
Chloride	Platelet count
Creatinine (with eGFR by Bedside Schwartz formula)	Differential WBC
	Urinalysis[a]:
Glucose	Specific gravity
Inorganic phosphate	pH
Magnesium	Protein
Potassium (primary endpoint)	Glucose
Sodium	Ketones
Total bilirubin	Blood
Total protein	Urobilinogen
	Leukocyte esterase
	Nitrites
	Bilirubin
	Other:
	Plasma parathyroid hormone
	Serum Fluoride
	Urine and Serum Pregnancy test (only for females of child-bearing potential)

[a] Urinalysis is not required for anuric subjects, see section 7.2.

Appendix D: Screening Schema