Patiromer Efficacy to Reduce Episodic Hyperkalemia in End Stage Renal Disease Patients Treated with Hemodialysis (PEARL-HD)

Protocol May 17, 2019

PI: John P. Middleton, MD

NCT03781089

1. Protocol Summary Synopsis

Name of Sponsor: Relypsa

Name of product: Patiromer

Title of Study: Patiromer Efficacy to Reduce Episodic Hyperkalemia in End Stage Renal Disease Patients Treated with Hemodialysis (PEARL-HD)

Study Center: Duke University

Study Period (weeks): 7

Study design: Prospective randomized open label trial

Primary objective: To determine if patiromer administered orally once a day with the morning or mid-day meal will reduce the frequency of episodes of hyperkalemia in ESRD patients who receive thrice-weekly HD.

Secondary objectives:

1. To determine whether patiromer can effectively be used in place of one dose of phosphate binder per day
2. To determine the between-group differences in percent of patients with serum K > 5.5 mEq/L
3. To determine the efficacy and dosing of patiromer in ESRD patients.
4. To determine the between-group differences in need for additional hemodialysis treatments due to hyperkalemia
5. To determine the between-group differences in pre-specified significant arrhythmia events as detected with cardiac monitors in Week 4.
6. To determine the between-group differences in serum albumin and PTH concentrations.
7. To determine feasibility of a large-scale hemodialysis-based trial.
8. To determine the change in serum potassium concentration two weeks after study drug is discontinued
9. To determine the change in serum phosphorus concentration two weeks after study drug has been discontinued
10. To develop procedures and instruments to be employed in a large scale clinical trial.

Planned enrollment: 40

Inclusion criteria:

1. Males and Females, age at least 18 years

2. End-stage renal disease treated with thrice-weekly hemodialysis for ≥ 3 months.

3. At least two measured pre-dialysis serum [K] ≥ 5.5 mEq/L or one [K] ≥ 6.0 mEq/L noted over the past three months

4. Current use of dialysate with potassium concentration = 2 mEq/L

5. Typical consumption of at least two meals per day

6. Have received customary dietary instruction over prior month

7. Considered by the treating physician(s) to be in otherwise stable clinical condition.

8. If patient is of childbearing potential, he/she will be willing to avoid pregnancy during the study using an acceptable birth control method.

Exclusion Criteria:

1. Not considered by the treating physician(s) to be adherent with recommended dialysis schedule and prescribed medications
2. Life expectancy < 3 months
3. Currently prescribed oral potassium supplements
4. Therapy with oral potassium-lowering medication in the prior three months,
5. Underlying severe gastrointestinal disorders, including history of ischemic bowel.
6. Corrected serum calcium concentration > 10.5 mg/dL in prior three months
7. Anticipated kidney transplant within the next 3 months
8. Prisoners or others who are involuntarily incarcerated or detained
9. Pregnant, breastfeeding, or considering pregnancy.
10. Participation in a clinical trial of an experimental treatment within the past 30 days

Duration of treatment:

Participants randomized to receive patiromer will receive the drug for a total of 4 weeks.

Withdrawal of subjects

Subjects will be withdrawn from the study and receive appropriate treatment for hyperkalemia (at the Investigator's discretion), if the serum potassium level exceeds 7 mEq/L during Week 2 to 7 and, the first sample is confirmed by a second sample exceeding 7 mEq/L at an unscheduled visit within one week.

Concomitant medications:

Subjects are not allowed to receive potassium binders during the study (e.g. sodium polystyrene sulfonate, or SPS) except in emergency situations.

Except for those listed in the exclusion criteria, all medications (prescription or over-the-counter) that have been started prior to screening may be continued during the course of the study.

Statistical analysis:

This is a proof-of-concept study, to determine the extent to which administration of patiromer has the potential to change the risk category for ESRD patients who are on conventional HD schedules. In addition, the study aims to develop and test study procedures and instruments that will be implemented in a large-scale clinical trial.

By nature of the size of the study, the power of the trial will be limited. The proposed primary endpoint is the between-group differences of the number of episodes, per subject, of serum K ≥ 5.5 mEq/L during Weeks 3 and 4. This will be assessed as follows: Six serum samples will be collected and assessed for each patient during the efficacy phase (Weeks 3 and 4). Patients would receive a score of perfect K control (6 of 6 samples in range; Score 1.0), moderate K control (5 of 6 in range; Score 0.83), inconsistent K control (4 of 6 in range; Score 0.67) , erratic K control (3 of 6 in range; Score 0.50), poor K control (2 of 6 in range; Score 0.33), very poor K control (1 of 6 in range; Score 0.17), or no K control (0 of 6 in range, Score 0). These scores will then

be averaged for the patients in the active treatment group and the control group, and the results will be compared. Using this approach, a sample size of n=20 per group provides 86% power to detect a between-group difference of 2 in mean episodes of hyperkalemia per patient, assuming $\alpha=0.05$ and standard deviation 2.

Exploratory endpoints, including those derived from the cardiac monitors, will be assessed by comparison of means and standard deviations between the two groups.

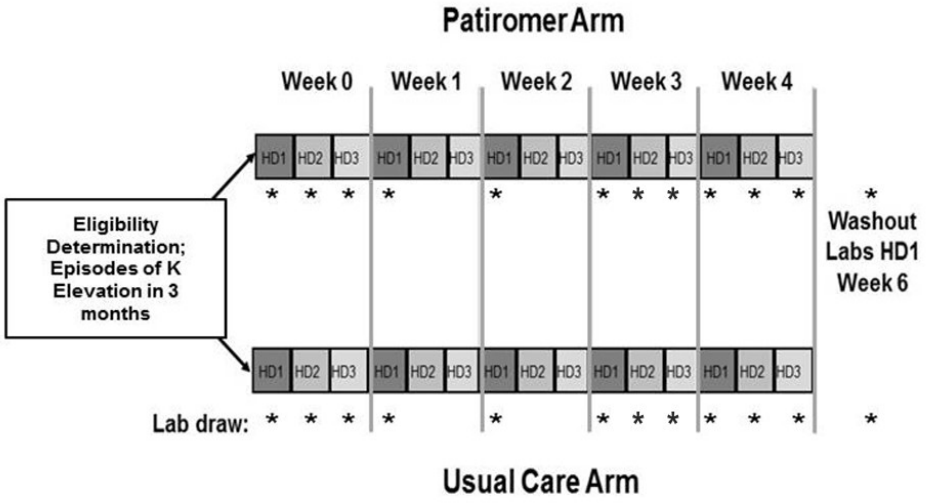
Safety Variables

Safety and tolerability variables will consist of adverse events, vital signs, ECG-parameters, clinical laboratory parameters and physical examination. Adverse Events will be summarized in an incidence table and coded to MedDRA. Laboratory parameters, vital signs and ECG-parameters will be summarized; the changes in the hematology, biochemistry parameters and vital signs from baseline will also be presented. Serious Adverse Events (SAE's) will be reported on a jointly developed form with Relypsa.

Efficacy Variables

Efficacy parameters will consist of serum levels of potassium, collected prior to scheduled dialysis treatments.

2. Study Flowchart



3. Introduction and Study Rationale

3.1 Problem of hyperkalemia

Patients with end stage renal disease (ESRD) who are treated with conventional hemodialysis (HD) schedules often exhibit life-threatening, episodic hyperkalemia. Reduced kidney function increases extracellular potassium concentration due to the combined effects of a net positive potassium balance in concert with disturbed ion distribution in the body fluid compartments [1] [2] In the HD population, scheduled measurement of serum potassium concentration is typically performed only once or twice a month. Even with this restricted testing schedule, serum potassium exceeds 5 mEq/L in more than a third of patients [3,4]. However, episodes of hyperkalemia are likely much more common during conventional HD, since many of these transient events are not captured with standard treatment and testing schedules. Episodic hyperkalemia disrupts the electrophysiology of heart muscle and can promote cardiac arrhythmias. It is plausible that episodes of hyperkalemia contribute to the alarmingly high rate of sudden cardiac arrest, by far the most common cause of death in the HD population [5,6] But consistent control of serum potassium levels is difficult in HD patients. Our own data suggest that 40-50% of HD patients who exhibit serum potassium concentrations > 5.5 mEq/L during routine measurements in one month will fail to be "cured" the following month with usual clinical care (unpublished data). One dilemma that arises is that reducing serum potassium with the use of low dialysate potassium is actually associated with an increased risk of sudden cardiac death [5]. Furthermore, HD patients already carry a high pill burden, and it is unclear if prescription of an additional oral medication will reduce the frequency of episodic hyperkalemia [7]. Even though the manner of achieving this ideal is unclear, these observations suggest that avoiding extremes in the concentrations of serum potassium will improve the cardiovascular risk in HD patients.

High serum potassium contributes to cardiac risk. Maintaining serum potassium homeostasis is critical to create a stable transmembrane potential of about -85 mV, and this permits normal cardiac and skeletal muscle function [8]. Abrupt changes in serum potassium levels result in deviations in membrane potential that can lead to muscle paralysis and to fatal arrhythmias [8] In patients with ESRD, the ability to maintain potassium balance by the kidney is diminished, and therefore acceptable potassium conditions can only be approximated by dietary potassium restriction and clearance with dialysis. In a patient maintained on a conventional, three-times-per-week HD regimen, potassium intake is recommended to be limited to about 60 mEq/day (420 mEq/week). Dialysis removal typically is around 70-100 mEq per treatment (210-300 mEq/week for thrice-weekly schedules)[2]. Assuming that native kidney function accomplishes minimal potassium clearance, to maintain a near-steady potassium concentration potassium elimination through the gastrointestinal tract is essential.

In the general population, the normal range for serum potassium is typically reported between 3.5 and 5.0 mEq/L but in HD patients the ideal serum potassium concentration tends to be higher. In a study of 2,134 HD patients, a pre-dialysis serum potassium level of 5.1 mEq/L was associated with the lowest risk of peri-dialytic sudden cardiac arrest, while potassium levels above and below 5.1 were associated with increasing risk [5]. Another study examining pre-dialysis serum potassium levels and survival within a cohort of 81,013 hemodialysis patients, potassium concentrations between 4.6-5.3 mEq/L were associated with the lowest incidence of all-cause mortality [9]nd a survey of 55,183 HD patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) multinational cohort confirmed that the lowest risk of death was observed among patients with serum potassium levels between 4 and 5.5 mEq/L and a significant increased risk of death and arrhythmia outcomes at potassium values ≥5.6 mEq/L [10] In a study of serum potassium values obtained within a large dialysis organization, approximately 20% of all serum potassium measurements were ≥5.5 mEq, and about 12.5% of measurements were ≥6.0, whereas potassium <4.0 accounted for only 9% of all measurements [4].

The removal of potassium from an individual receiving conventional HD departs dramatically from the physiology of a person who has normal kidney function. First of all, HD can only remove potassium from the extracellular fluid compartment, which contains just 2% of total body potassium [2]. Second, the rate of lowering of serum potassium concentration is inconstant, causing a rapid fall in serum potassium at the start of the HD treatment when the serum-to-dialysate gradient is highest. The abrupt drop in the first hour is followed by more gradual decline over next 2-3 hours, as the serum-to-dialysate potassium gradient narrows [11]. The final serum potassium concentration approaches that delivered in the dialysate. Third, the end of the HD session causes a subacute "rebound" of serum potassium levels as potassium mobilizes from the intracellular to the extracellular space. The magnitude and the time course of these potassium transients over the HD period are influenced by the initial serum potassium concentrations as well as by the other constituents of the dialysis prescription such as the amount of volume ultrafiltration, dialysate bicarbonate, glucose, and potassium concentrations [12]. The potential impact of excursions of potassium concentrations is compelling. In a study of ESRD patients on conventional treatment schedules who had wearable defibrillators in place, 70.0% of the captured arrhythmia events occurred during the HD session and 2.8% arrhythmias were observed immediately after the dialysis procedure [13].

It might seem as if the problem of hyperkalemia in ESRD can be managed by setting a very low dialysate potassium concentration. However, potential hazards may arise by reducing serum potassium levels too rapidly during HD treatments [14]. Clearly a lack of consensus exists on the ideal dialysate potassium concentration to prescribe. Recent data from DOPPS reported the range of prevalent use of potassium dialysate <2 mEq/L from as low as 3% in the US to as high as 62% in Spain [10]. The safety of low potassium dialysate has been a focus of concern given the possibility that dialysis-induced potassium reductions may provoke cardiac arrhythmias and sudden cardiac death. Multiple large retrospective studies investigated associations between dialysate potassium levels, serum potassium levels, and risk of sudden death, cardiac events, and all-cause mortality. In general, large cohort studies identified increased risks of sudden cardiac death associated with use of low potassium dialysate < 2 mEq/L [5,9]. The risks associated with low potassium dialysate are principally seen among patients with low to normal pre-dialysis serum potassium. No long-term, prospective, controlled studies have been conducted to examine the effect of low potassium dialysate on hard clinical outcomes, but several short term trials employed cardiac monitors to measure subclinical arrhythmic events such as ventricular ectopy, premature ventricular complexes, and changes in electrocardiographic conduction parameters [13,15]. Most but not all studies observed higher rates of ventricular ectopy and QTc interval prolongation associated with exposure to potassium dialysates of 0 or 1 mEq/L compared to higher potassium dialysate concentrations [14 16,17]. However, whether these observations also apply to clinical arrhythmic events or mortality is not known. In summary, circumstantial evidence highlights the hazards of using a low potassium dialysate <2 mEq/L, and the evidence for risk is strongest for patients with serum potassium levels <5 mEq/L. Whether lower potassium dialysate is appropriate or potentially beneficial for patients with higher serum potassium levels is unclear.

Alternatively, hyperkalemia in ESRD patients can potentially be managed with oral medications which can bind potassium. Sodium polystyrene sulfonate (SPS) has been available since the 1950s to treat high serum potassium levels, and it is approved for treatment of hyperkalemia by the US Food and Drug Administration (FDA) [18]. However, SPS has not been rigorously studied. There is limited prospective, long-term clinical trial data available to understand the safety and efficacy of these agents, particularly in patients with ESRD. Patients experience adverse gastrointestinal symptoms with SPS, and its use has been associated with life-threatening colonic necrosis [19-21]. In addition, a significant sodium load can occur with SPS, and this can be a particular concern in patients with ESRD [22,23] These issues make the repeated or chronic administration of SPS not feasible, particularly in patients such as those with ESRD where the incidence of hyperkalemia is high. A safe and effective oral potassium binder has the potential to reduce the frequency of episodes of hyperkalemia and to limit large excursions in serum potassium values in ESRD patients treated with hemodialysis.

3.2 Clinical experience with patiromer

Relypsa recognized a need for a well-tolerated potassium binder to be used in both acute and chronic clinical settings. Relypsa developed an orally administered, non-absorbed, high-capacity serum potassium binder with physicochemical characteristics that might yield an effective product suitable for chronic use. Patiromer is composed of patiromer sorbitex calcium, a new chemical entity belonging to the pharmacologic class of Potassium Binders, and xanthan gum. The product consists of the polymer anion and a calcium-sorbitol counter-ion. The polymer anion is also termed "patiromer anion" or simply "patiromer," and it is the active moiety. The resin is a cation-exchange polymer that binds potassium predominantly in the lumen of the colon where active potassium secretion occurs. This potassium binding leads to fecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels in the hyperkalemic patient. On October 21, 2015 the US FDA approved patiromer for use in patients with elevated potassium concentration in the body, based on data described below in section 3.4. The approved indication in the US for patiromer is the treatment of hyperkalemia.

3.3 Study rationale

Patients with ESRD who are treated with three times per week with HD are commonly exposed to the risk of high potassium in the blood (hyperkalemia). Serum potassium values above 5.5 mEq/L are associated with increased mortality. Hyperkalemia treatment options are limited in the ESRD population. The use of SPS is associated with poor patient tolerance and with serious adverse clinical risks; the prescription of low potassium dialysate (<2mEq/L) is associated with increased risk of cardiac arrest. Oral administration of patiromer is effective to decrease serum potassium in patients who have CKD and hyperkalemia, but it has not been studied extensively in HD patients. Either hyperkalemia or excursions in serum potassium concentrations may play a role in the high risk of sudden cardiac death in ESRD patients treated with HD. It is not known if once-daily dosing of patiromer will reduce the frequency of episodes of hyperkalemia in this vulnerable population.

It is important to review standard, usual care for ESRD patients who are treated with conventional HD schedules (thrice-weekly treatments), to avoid and treat episodes of hyperkalemia. If patients present at an emergency facility or hospital and are discovered to have hyperkalemia, they are typically treated with inhaled beta agonists, intravenous glucose and insulin, and/or intravenous calcium [24]. The latter does not treat the hyperkalemia *per se*, but it is intended to stabilize the myocardial cells and limit risk of depolarization. A single dose of SPS is often administered. If these medical interventions fail to resolve hyperkalemia, urgent hemodialysis is prescribed. In the outpatient setting, hyperkalemia may be detected at the start of the HD session. If there are no symptoms, patients receive hemodialysis with their usual prescriptions and no further interventions are prescribed. For all patients, the HD clinic-based dietitian will counsel on adherence with a low potassium diet, with the goal of limiting potassium intake to less than 60 mEq per day [25,26]. For this current protocol, the dietitian will be blinded to the assigned treatment for the course of the study. If pre-dialysis hyperkalemia is a recurrent problem, the physician and dialysis clinic team will review the prescribed dialysate. Due to the risk associated with prescription of low dialysate potassium, the outpatient clinics employed in this study do not prescribe dialysate potassium lower than than 2 mEq/L. In rare instances, if hyperkalemia continues to recur despite these interventions, and additional HD treatments will be prescribed.

3.4 Dosing rationale

Three clinical studies primarily inform the recommended initial dose and titration of patiromer in those participants in this study who randomize to receive the drug. In the first study, 243 patients with chronic kidney disease (CKD) and hyperkalemia initially were treated with patiromer [27]. The starting dose was 8.4 or 16.8 g (as divided doses BID) for four weeks. With a mean daily dose of patiromer during the initial treatment phase of 12.8 g in patients with mild hyperkalemia and 21.4 g in patients with moderate-to-severe hyperkalemia, 76% of the participants reached the target range of serum potassium (3.8-5.1 mEq/L). Then the study had an 8-week period of randomized withdrawal from patiromer in 107 subjects. In the latter period, hyperkalemia occurred in 60% of the placebo-treated patients and only 15% of the patients who continued on patiromer [27]. In the second study, 304 subjects with hyperkalemia, CKD, type 2 diabetes, and hypertension were randomized to receive 1 of 3 randomized starting doses of patiromer (4.2 g [n = 74], 8.4 g [n = 74], or 12.6 g [n = 74] twice daily [mild hyperkalemia] or 8.4 g [n = 26], 12.6 g [n = 28], or 16.8 g [n = 30] twice daily [moderate hyperkalemia]) [28]. Patiromer was titrated to achieve and maintain serum potassium level 5.0 mEq/L or lower. At the end of the open label 52-week study the mean reduction from baseline in serum potassium level at week 4 in patients with mild hyperkalemia was 0.35 mEq/L for the 4.2 g twice daily starting-dose group, 0.51 mEq/L for the 8.4 g twice daily starting-dose group, and 0.55 mEq/L for the 12.6 g twice daily starting-dose group [28]. From week 4 through week 52, statistically significant mean decreases in serum potassium levels were observed at each monthly point in patients with mild and moderate hyperkalemia. The mean daily dose of patiromer after 4 weeks was 18.5 g for the patients with mild hyperkalemia and 26.9 g with moderate hyperkalemia.

The third relevant trial was the only study published to date that enrolled HD patients. In this study, six ESRD patients on HD were monitored for a 7-day baseline period, then they were administered patiromer 4.2g TID [29]. In this small study, the mean serum potassium decreased from 5.79 ± 0.31 mEq/L at baseline to 5.39 mEq/L during treatment, a mean decrease = 0.4 mEq/L (p=0.08). The mean fecal potassium excretion increased from 616 ± 203 mg/day during baseline to 975 ± 399 mg/day during treatment (P=0.02). The proportion of days with serum potassium < 5.5 mEq/L was 38% during the baseline period and 67% during the treatment period..

This current protocol includes an initial dose of patiromer of 8.4g once daily to be administered with the morning or mid-day meal. This will be titrated according to the pre-dialysis potassium values in weeks 1, 2 and 3 of the protocol.

3.5 Adverse events with patiromer

In the published clinical trial of patiromer that was the longest duration (52 weeks), hypomagnesemia (7.2%) was the most common treatment-related adverse event, mild to moderate constipation (6.3%) was the most common gastrointestinal adverse event, and hypokalemia (<3.5 mEq/L) occurred in 5.6% of patients [28].

3.6 Potential for drug-drug interactions with patiromer

Patiromer has the potential to bind many orally administered medications. However, few formal drug interaction studies have been conducted in humans. The package insert notes that twenty-eight drugs were tested to determine the potential for interaction with patiromer. Fourteen of the drugs tested did not show an *in vitro* interaction with patiromer (acetylsalicylic acid, allopurinol, amoxicillin, apixaban, atorvastatin, cephalexin, digoxin, glipizide, lisinopril, phenytoin, riboflavin, rivaroxaban, spironolactone and valsartan). Twelve of the 14 drugs that showed an *in vitro* interaction were subsequently tested *in vivo*. The package insert cites studies in healthy volunteers which showed that patiromer did not alter the systemic exposure of amlodipine, cinacalcet, clopidogrel, furosemide, lithium, metoprolol, trimethoprim, verapamil or warfarin when coadministered. Patiromer decreased the systemic exposure of co-administered ciprofloxacin, levothyroxine and metformin.

However, there was no interaction when patiromer and these drugs were taken three hours apart. To account for this, patiromer should be adminstered at least 3 hours before or 3 hours after other oral medications.

4. Study objectives

4.1 Primary endpoint

To determine if patiromer administered orally once a day with the morning or mid-day meal will reduce frequency of episodes of hyperkalemia in ESRD patients who receive thrice-weekly HD.

4.2 Secondary endpoints

1. To determine whether patiromer can effectively be used in place of one dose of phosphate binder per day
2. To determine the between-group differences in percent of patients with serum K > 5.5 mEq/L
3. To determine the efficacy and dosing of patiromer in ESRD patients.
4. To determine the between-group differences in need for additional hemodialysis treatments due to hyperkalemia
5. To determine the between-group differences in pre-specified significant arrhythmia events as detected with cardiac monitors in Week 4.
6. To determine the between-group differences in serum albumin and PTH concentrations.
7. To determine feasibility of a large-scale hemodialysis-based trial.
8. To determine the change in serum potassium concentration two weeks after study drug is discontinued
9. To determine the change in serum phosphorus concentration two weeks after study drug has been discontinued
10. To develop procedures and instruments to be employed in a large scale clinical trial.

5. Selection and withdrawal of subjects

5.1. Informed consent

The Investigator, or a person designated by the Investigator, will fully inform the subject of all pertinent aspects of the study including the written information which has been reviewed and approved by the Institutional Review Board (IRB).

Prior to a subject's participation in the study, the Informed Consent Form will be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

The Informed Consent Form used by the Investigator for obtaining the subject's informed consent will be the IRB approved version.

5.2. Inclusion criteria

1. Males and Females, age at least 18 years

2. End-stage renal disease treated with thrice-weekly hemodialysis for ≥ 3 months.

3. At least two measured pre-dialysis serum [K] ≥ 5.5 mEq/L or one [K] ≥ 6.0 mEq/L noted over the past three months

4. Current use of dialysate with potassium concentration = 2 mEq/L

5. Typical consumption of at least two meals per day

6. Have received customary dietary instruction over prior month

7. Considered by the treating physician(s) to be in otherwise stable clinical condition.

8. If patient is of childbearing potential, he/she will be willing to avoid pregnancy during the study using an acceptable birth control method.

5.3. Exclusion criteria

1. Not considered by the treating physician(s) to be adherent with recommended dialysis schedule and prescribed medications

2. Life expectancy < 3 months

3. Currently prescribed oral potassium supplements

4. In the prior three months, therapy with oral potassium-lowering medication

5. Underlying severe gastrointestinal disorders, including history of ischemic bowel.

6. Serum potassium concentration > 7 mEq/L in prior three months

7. Anticipated kidney transplant within the next 3 months

8. Prisoners or others who are involuntarily incarcerated or detained

9. Pregnant, breastfeeding, or considering pregnancy.

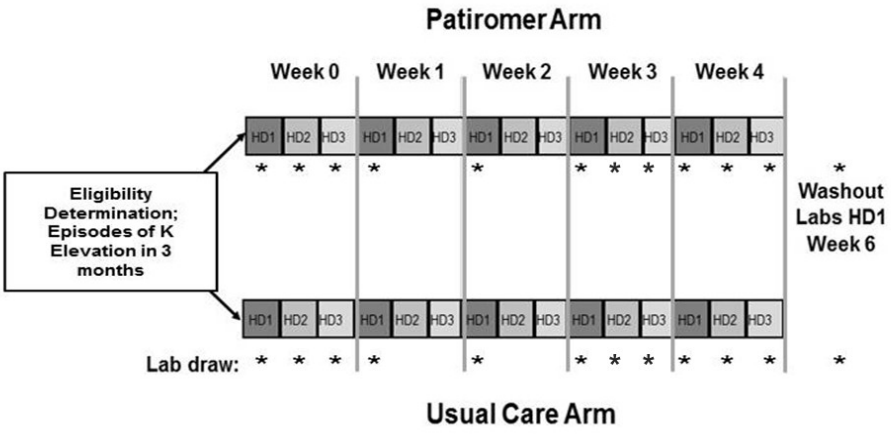
10. Participation in a clinical trial of an experimental treatment within the past 30 days

6. Trial design

6.1 Number of subjects

40 patients will be enrolled in the study.

6.2 Study flow chart



48-hour cardiac monitors will be placed for each subject over the three-day interdialytic interval and in the HD2-HD3 interval of Week 0 and Week 4. An Electrocardiogram (ECG) will also occur in week 0.

6.3 Determination of eligibility

The study team will review records of prevalent Duke patients in the DaVita outpatient dialysis facilities. Patient eligibility will be determined. If routine measurements of serum potassium indicate either at least two measured pre-dialysis serum [K] ≥ 5.5 mEq/L or one [K] ≥ 6.0 mEq/L noted over the preceding three months, patients medical record will be reviewed to determine whether the remaining inclusion and exclusion criteria are met. The physician rounding in the dialysis unit will be asked if it is suitable to approach the patient. Eligible patients will be approached for the informed consent process.

6.4. Consent

Patients will be provided the Informed Consent Form and this will be reviewed by the Study Personnel. Patients will be encouraged to take the form home and review with their family if possible

6.5 Baseline period, Week 0

Once a patient has signed the ICF, a 12 lead ECG will be obtained. The long term cardiac monitor will be placed at the end of HD3 prior to Week 0 and removed at the beginning of HD3 of Week 0. Weight, pulse, and blood pressure will be recorded. Medical history and demographic data will be collected. Medications will be recorded. The hemodialysis prescription for target weight and dialysate potassium and calcium will be recorded.

Before each hemodialysis session in Week 0, blood samples will be collected and sent to the clinical laboratory. The Renal Function Panel and magnesium levels will be determined with these samples before the first dialysis session of the week (HD1). Serum pregnancy test will be measured for females of child-bearing potential.

6.6 Randomization

Randomization will occur at any time in Week 0 prior to HD3. This will be done using the REDCap system and will assign patients 1:1 to either continue usual care or to receive patiromer as detailed below.

6.7 Open-label patiromer and dose titration, Weeks 1, Week 2, Week 3, Week 4.

Patients randomized to the patiromer arm will initiate on 8.4 g/day (one pack) given once a day with breakfast or lunch, to start after HD3 at the end of Week 0. The patient is instructed to not take any other medications for three hours before or three hours after patiromer.

The patiromer dose will be titrated based on serum potassium concentrations on HD1 of weeks 1, 2, and 3. Patiromer will be increased by 8.4 g/day if K ≥ 5.5 meq/L, decreased by 8.4 g/day if K < 4.5 mEq/L, and patiromer will be discontinued if K < 4 mEq/L.

6.8 Usual care group

Patients randomized to the usual care arm will undergo monitoring with laboratory measurements as outlined in the study protocol (6.13: Follow-up evaluations Weeks 1, 2 and 6.14: The assessment period Weeks 3, 4 and 6). The patients will continue to have standard of care (SOC) monitoring by the study team and by the dialysis care team. They will continue to have SOC teaching and follow-up with the renal dietitian in the clinic.

6.9 Therapies for all randomized patients thoughout the study

For all study participants, the dialysis prescription will not be changed throughout study. ACE inhibitor and angiotensin receptor blocker medications will be unchanged throughout study. Calcitriol or active vitamin D analogues, nutritional vitamin D, calcimimetics, multivitamins, and prescribed phosphate binder medication will be managed by the rounding clinician throughout study and will not be altered by the study protocol.

All patients will be provided oral instructions at the start of the trial on adherence with low potassium diets. All patients will receive dietary instruction from the clinic dietitian, with the goal of limiting potassium intake to less than 60 mEq per day. This is the standard of care. The clinic dietitian will be blinded to the patient group assignment in the study. Subjects will be encouraged not to change their food and diet habits during the study period. The prescription of other oral potassium binders will be prohibited in the study. All study participants will also be given a printed flyer for instruction on a low potassium diet.

6.10 Seven day cardiac monitor

The long-term heart monitor (LTHM) to be used in this study is a dual –channel wearable cardiac monitor that is applied as a skin patch. The Medicomp Telepath records cardiac rhythms for up to 7 days (medicompinc.com; last accessed 5/1/19).

The first LTHM, Telepatch #1 will be applied at the end of HD3 prior to Week 0 and removed at the beginning of HD3 of Week 0. The second LTHM, Telepatch #2, will be applied at the end of HD3 at the end of HD3 and removed at the beginning of HD3 of Week 4.

When the cardiac monitor is applied to a patient, a user guide and a symptom diary will be provided.

6.11 Electrocardiography (ECG)

A 12 lead ECG will be performed during Week 0. The patient will go to an outpatient Duke cariology clinic for the ECG.

6.12 Concomitant medications

Except for those listed in the exclusion criteria, all medications (prescription or over-the-counter) initiated prior to enrollment may be continued during the course of the study.

All medications that are continued from the start of the study or that are started during the study (other than the study medication) including prescription or over-the-counter will be documented by the study team.

6.13 Follow-up evaluations Weeks 1, 2

A member of the study team will see the patient at the start of HD1 Week 1. Weight, pulse and blood pressure will be recorded. A pre-dialysis serum potassium lab sample will be collected and sent to the clinical lab. Concomitant medications will be recorded.

With study team visit on HD2 or HD3 of Week 1, the patiromer dose will be titrated based on the pre-dialysis potassium measured at HD1. Patiromer will be increased by 8.4 g/day if K ≥ 5.5 meq/L, decreased by 8.4 g/day if K < 4.5 mEq/L, and patiromer will be discontinued if K < 4 mEq/L.

6.14 The assessment period Weeks 3, 4 and 6

A member of the study team will see the patient at the start of HD1 Week 3 and HD1 Week 4. Weight, pulse and blood pressure will be recorded. A pre-dialysis serum potassium lab sample will be collected and sent to the clinical lab to measure potassium. Concomitant medications will be recorded.

With study team visit on HD1 of Week 3, the patiromer dose will be titrated based on the pre-dialysis potassium measured at HD1. Patiromer will be increased by 8.4 g/day if K ≥ 5.5 meq/L, decreased by 8.4 g/day if K < 4.5 mEq/L, and patiromer will be discontinued if K < 4 mEq/L.

The long term heart monitor (LTHM; Telepatch #2) will be placed at the end of HD3 Week 3 and removed at the beginning of HD3 of Week 4.

With study team visit on HD1 of Week 6, weight, pulse and blood pressure will be recorded. A pre-dialysis blood sample will be collected and sent to the clinical lab for a renal function panel. Concomitant medications will be recorded.

6.15. Withdrawal of subjects.

A subject may discontinue participation in the study at any time without being obligated to give a reason, although they are free to do so if they wish.

If a subject does withdraw from the study, the Investigator must make every effort to perform all post-study assessments. Safety and tolerability data on the subject will be evaluated and reported. The Investigator may withdraw a subject due to non-compliance with the protocol requirements, or if an event occurs which would interfere with the objectives of the study.

Subjects must be withdrawn from the study if:

1. Informed consent is withdrawn voluntarily by the subject.

2. The Investigator believes it is in the best interest of the subject to be removed from the study.

3. The serum potassium levels exceeds 7 mEq/L during Week 2 to 7 and, the first sample is confirmed by a second sample exceeding 7 mEq/L at an unscheduled visit within one week.

4. A serious adverse event occurs (the Investigator must consider severity of the event and relatedness to study medication).

5. A significant protocol violation occurs.

The date and reason for discontinuation must be noted and a brief discontinuation summary must be filled out. Serious Adverse Events should be followed up until resolution or for 30 days after discontinuation. All efforts should be made to have subjects that discontinue from study return the remainder of their study medication.

6.16. Replacement of subjects

Subjects who are withdrawn will not be replaced.

7. Study medication

7.1 Description of medication

Patiromer is provided as a single-use packet containing a powder that can be suspended in water for oral administration. Patiromer is an off-white to light-brown powder; occasional white particles may be present. Each packet contains 8.4 g patiromer. Patiromer will be provided free of charge to study participants. Once the study is over, the remaining patiromer will be returned to Relypsa.

7.2 Treatment dispensing and administration

The coordinator will provide patiromer packets as outlined to the study participants who randomize to receive the study medication. The patient will be written instructions to take patiromer as follows:

- Measure ~1/3 cup of water. Pour half of the water into a glass, then add patiromer and stir. Add the remaining water and stir thoroughly. The powder will not dissolve completely and the mixture will look cloudy.
- Drink the mixture immediately. If powder remains in the glass after drinking, add more water, stir and drink immediately. Repeat as needed to ensure the entire dose is administered.
- Patiromer can be mixed with water, apple juice, or cranberry juice. Prepare each dose 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.

7.3. Storage requirements

Patiromer will be stored in the refrigerator at 2°C – 8°C (36°F – 46°F). If stored at room temperature (25°C ± 2°C [77°F ± 4°F]), patiromer must be used within 3 months of being taken out of the refrigerator. For either storage condition, do not use patiromer after the expiration date printed on the packet. Avoid exposure to excessive heat above 40°C (104°F).

8. Statistics

8.1. Primary analysis

This is a proof-of-concept study, to determine the extent to which administration of patiromer has the potential to change the risk category for ESRD patients who are on conventional HD schedules. In addition, the study

aims to develop and test study procedures and instruments that will be implemented in a large-scale clinical trial.

By nature of the size of the study, the power of the trial will be limited for the primary analysis. The proposed primary endpoint is the between-group differences of the number of episodes, per subject, of serum K ≥ 5.5 mEq/L during Weeks 3 and 4. This will be assessed as follows: Six serum samples will be collected and assessed for each patient during the efficacy phase (Weeks 3 and 4). Patients would receive a score of perfect K control (6 of 6 samples in range; Score 1.0), moderate K control (5 of 6 in range; Score 0.83), inconsistent K control (4 of 6 in range; Score 0.67), erratic K control (3 of 6 in range; Score 0.50), poor K control (2 of 6 in range; Score 0.33), very poor K control (1 of 6 in range; Score 0.17), or no K control (0 of 6 in range, Score 0). These scores will then be averaged for the patients in the active treatment group and the control group, and the results will be compared. Using this approach, a sample size of n=20 per group provides 86% power to detect a between-group difference of 2 in mean episodes of hyperkalemia per patient, assuming α=0.05 and standard deviation 2.

8.2 Secondary endpoints

Because study sample size is limited and is based only on the amount of information needed to adequately assess the primary hypothesis, this pilot study will have limited power to effects on secondary endpoints. We consider these measurements to be exploratory. A significant effect on the exploratory endpoints will be considered in light of the results of the primary analysis.

Differences in laboratory values between the treatment groups will be determined by analysis of variance (ANOVA). The long-term heart monitor results will be compared in the following ways:

Group 1: Individual patient compared by their LTHM #1 vs LTHM #2;

Group 2: Individual patient compared by their LTHM #1 vs LTHM #2

Group 1 LTHM #1 vs Group 2, LTHM #1;

Group 1 LTHM #2 vs Group 2, LTHM #2

Each monitor will be assigned a point score, counting only the most severe event.

Finding	**Score**
Sustained VT, VF and/or asystolic cardiac arrest (CPR required)	10
Nonsustained VT (≥ 3 beats but < 30 seconds) **and/or** > 5 second pause during daytime (0800-2000) **and/or** atrial fibrillation (> 30 seconds)	3
PVC > 1000/24h and/or > 3 second pause during daytime (0800-2000)	2
PVC >500/24h and/or or HR < 40 for 5 consecutive beats during daytime (0800-2000)	1

Monitor period scores will be tabulated, and differences in period scores addressed by ANOVA.

Heart rate variability will be recorded in time-domains from the LTHM and periods will be compared.

The QT intervals will be compared for the LTHM periods in two different procedures. The mean QTc will be determined for each 7 day period, and groups will be compared. In addition, in the LTHM will collect 30 second rhythm strips in the last dialysis session (HD3) of week 4, and QTc will be determined and compared between the treatment groups.

Bradyarrhythmias will be recorded and classified for comparison as follows: asystole > 5 seconds with syncope, third degree AV block, second degree AV block, sinus pause > 3 seconds, and sinus bradycardia < 40 bpm.

9. Monitoring

The sponsor of the study, Relypsa, will provide study monitoring at a mutally agreeable time, during normal business hours.

10.. Schedule of Assessments

Procedures/Visits	Pre-Week 0	Week 0			Week 1			Week 2			Week 3			Week	
Visit		HD1	HD2	HD3	HD1	HD2	HD3	HD1	HD2	HD3	HD1	HD2	HD3	HD1	HD2
Week		1			2			3			4			5	
Determination of Elevated K Episodes	X														
Informed Consent	X														
Medical History and Demography		X													
Randomization[1]				X											
Initiation of Patiromer[2]				X											
Patiromer titration[3]						X			X			X			
Physical Exam		X													
Vital Signs[4] (BP, HR, Height, Weight)		X			X			X			X			X	
Renal Function Panel		X													
Serum Potassium			X	X	X			X			X	X	X	X	X
Serum Magnesium		X						X			X			X	
Serum Pregnancy Test[5]		X													
Holter Monitor Applied	X												X		
Holter Monitor Removed				X											
Previous medication and concomitant medication		X	X	X	X			X			X			X	X
Adverse Event Questioning		X	X	X	X			X			X		X	X	X
Dialysis[6]															
ECG	X	←									→				

1=Randomization can occur at any point after Week 0 HD1 as long as it is completed prior to Week 0, HD3.

2=If randomized to the Patiromer Arm

3=Patiromer will be increased by 8.4 g/day if K≥5.1 mEq/L, decreased by 8.4 g/day if K<4.0 mEq/L, and discontinued if K<3.5mEq/L

4= Blood Pressure taken after sitting for 5 minutes; Height only collected at Week 0, HD1

5=Females of child bearing potential

6= Hemodialysis should be performed 3 times per week

BIBLIOGRAPHY

1. Agar BU, Culleton BF, Fluck R, Leypoldt JK. Potassium kinetics during hemodialysis. *Hemodialysis international International Symposium on Home Hemodialysis.* 2015;19(1):23-32.
2. Sanghavi S, Whiting S, Uribarri J. Potassium balance in dialysis patients. *Seminars in dialysis.* 2013;26(5):597-603.
3. Pun PH, Middleton JP. Sudden cardiac death in hemodialysis patients: a comprehensive care approach to reduce risk. *Blood purification.* 2012;33(1-3):183-189.
4. Brunelli SM, Du Mond C, Oestreicher N, Rakov V, Spiegel DM. Serum Potassium and Short-term Clinical Outcomes Among Hemodialysis Patients: Impact of the Long Interdialytic Interval. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2017;70(1):21-29.
5. Pun PH, Lehrich RW, Honeycutt EF, Herzog CA, Middleton JP. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. *Kidney international.* 2011;79(2):218-227.
6. System USRD. *2017 USRDS annual data report: Epidemiology of kidney disease in the United States.* Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017.
7. McIntyre C, McQuillan R, Bell C, Battistella M. Targeted Deprescribing in an Outpatient Hemodialysis Unit: A Quality Improvement Study to Decrease Polypharmacy. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2017;70(5):611-618.

8. Weiss JN, Qu Z, Shivkumar K. Electrophysiology of Hypokalemia and Hyperkalemia. *Circulation Arrhythmia and electrophysiology.* 2017;10(3).
9. Kovesdy CP, Regidor DL, Mehrotra R, et al. Serum and dialysate potassium concentrations and survival in hemodialysis patients. *Clinical journal of the American Society of Nephrology : CJASN.* 2007;2(5):999-1007.
10. Karaboyas A, Zee J, Brunelli SM, et al. Dialysate Potassium, Serum Potassium, Mortality, and Arrhythmia Events in Hemodialysis: Results From the Dialysis Outcomes and Practice Patterns Study (DOPPS). *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2017;69(2):266-277.
11. Pun PH, Goldstein BA, Gallis JA, Middleton JP, Svetkey LP. Serum Potassium Levels and Risk of Sudden Cardiac Death Among Patients With Chronic Kidney Disease and Significant Coronary Artery Disease. *Kidney international reports.* 2017;2(6):1122-1131.
12. Pun PH, Middleton JP. Dialysate Potassium, Dialysate Magnesium, and Hemodialysis Risk. *Journal of the American Society of Nephrology : JASN.* 2017;28(12):3441-3451.
13. Wan C, Herzog CA, Zareba W, Szymkiewicz SJ. Sudden cardiac arrest in hemodialysis patients with wearable cardioverter defibrillator. *Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc.* 2014;19(3):247-257.
14. Hou S, McElroy PA, Nootens J, Beach M. Safety and efficacy of low-potassium dialysate. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 1989;13(2):137-143.
15. Roy-Chaudhury P, Tumlin JA, Koplan BA, et al. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. *Kidney international.* 2018;93(4):941-951.
16. Santoro A, Mancini E, Gaggi R, et al. Electrophysiological response to dialysis: the role of dialysate potassium content and profiling. *Contributions to nephrology.* 2005;149:295-305.
17. Santoro A, Mancini E, London G, et al. Patients with complex arrhythmias during and after haemodialysis suffer from different regimens of potassium removal. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2008;23(4):1415-1421.
18. Kayexalate® SODIUM POLYSTYRENE SULFONATE, USP Cation-Exchange Resin Package Insert. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2009.
19. Yuan CM, Nee R, Little DJ, Abbott KC. Incidence of sodium polystyrene sulfonate-associated colonic necrosis. *The American journal of medicine.* 2013;126(9):e13.
20. Bomback AS, Woosley JT, Kshirsagar AV. Colonic necrosis due to sodium polystyrene sulfate (Kayexalate). *The American journal of emergency medicine.* 2009;27(6):753.e751-752.
21. Chou YH, Wang HY, Hsieh MS. Colonic necrosis in a young patient receiving oral kayexalate in sorbitol: case report and literature review. *The Kaohsiung journal of medical sciences.* 2011;27(4):155-158.
22. Watson MA, Baker TP, Nguyen A, et al. Association of prescription of oral sodium polystyrene sulfonate with sorbitol in an inpatient setting with colonic necrosis: a retrospective cohort study. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2012;60(3):409-416.
23. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *Journal of the American Society of Nephrology : JASN.* 2010;21(5):733-735.
24. Allon M. Hyperkalemia in end-stage renal disease: mechanisms and management. *Journal of the American Society of Nephrology : JASN.* 1995;6(4):1134-1142.
25. Shingarev R, Allon M. A physiologic-based approach to the treatment of acute hyperkalemia. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2010;56(3):578-584.
26. Putcha N, Allon M. Management of hyperkalemia in dialysis patients. *Seminars in dialysis.* 2007;20(5):431-439.
27. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *The New England journal of medicine.* 2015;372(3):211-221.
28. Bakris GL, Pitt B, Weir MR, et al. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. *Jama.* 2015;314(2):151-161.
29. Bushinsky DA, Rossignol P, Spiegel DM, et al. Patiromer Decreases Serum Potassium and Phosphate Levels in Patients on Hemodialysis. *American journal of nephrology.* 2016;44(5):404-410.