Drug Substance	sodium zirconium cyclosilicate (added to dialysate)
Study Number	NN-007 (ADAPT)
Company Reference	D9480C00024
Version	4.0 (Amendment 2)
Date	28 April 2022

A Prospective, RanDomized, Multi-Center, Open-Label, Cross-Over Study of Sodium Zirconium Cyclosilicate to Control Interdialytic HyperkalemiA Following Augmentation of Dialysate Potassium: Efficacy to Reduce the Incidence of Post-Dialysis Atrial Fibrillation and Clinically SignificanT Cardiac Arrhythmias - ADAPT Trial

Sponsor:

NephroNet Inc.

575 Professional Drive, Suite 260

Atlanta, GA 30046

Contact: James Tumlin, MD

Cell: 770-490-9203

Email: JamesTumlinMD@nephronet.com

VERSION HISTORY

Version 1.0, 11 November 2021
Superseded by Version 2.0, February 2022. **Note:** This version was not submitted to the Institutional Review Board.
Version 2.0, 16 February 2022
Initial creation with Piccolo Testing System Update
Version 3.0 (Amendment 1), 06 April 2022
• Clarifications and/or minor changes made to the following: ➢ Study Objective and Outcome Measures ➢ Inclusion/Exclusion Criteria ➢ Schedule of Assessments ➢ LINQ Insertable Cardiac Monitor ➢ Blood Draws and Standard of Care Laboratory Testing ➢ Investigational Product (removal of 10 gram packet) ➢ Administrative Updates
Version 4.0 (Amendment 2), 28 April 2022
• Clarifications and/or minor changes made to the following: ➢ Safety Objectives ➢ Exclusion Criteria ➢ Schedule of Assessments and Footnotes ➢ Assignment of Subject Numbering ➢ Blood Draws and Standard of Care Laboratory Testing ➢ Administrative Updates

PROTOCOL SYNOPSIS

A Prospective, RanDomized, Multi-Center, Open-Label, Cross-Over Study of Sodium Zirconium Cyclosilicate to Control Interdialytic HyperkalemiA Following Augmentation of Dialysate Potassium: Efficacy to Reduce the Incidence of Post-Dialysis Atrial Fibrillation and Clinically SignificanT Cardiac Arrhythmias - ADAPT Trial

National Coordinating Investigator:

James A. Tumlin, MD

Professor of Medicine, Emory University School of Medicine, Atlanta

President, NephroNet Inc.

Nephrologist, Georgia Nephrology, LLC

575 Professional Drive Suite 260

Atlanta GA, 30046

Tel: 770-490-9203

E-mail: JamesTumlinMD@nephronet.com

Study site(s) and number of subjects planned

Planned number of sites: Approximately 10 - 12

Planned number of patients randomized: 88

Average number of patients randomized per site: approximately 9

(No minimum or maximum number of enrolled subjects will be specified.)

Study design

This is a prospective, open-labelled, randomized, 2x2 cross-over design study of 88 patients with end stage renal disease (ESRD) receiving routine out-patient dialysis using a standard 2.0 potassium ion (K^+)/2.5 calcium ion (Ca^{++}) dialysate bath. The overall aim of the study is to determine whether converting stable hemodialysis patients from a "standard" 2.0 K^+/2.5 Ca^{++} dialysate (without Lokelma) to a 3.0 K^+/2.5 Ca^{++} mEq dialysate supplemented with the orally administered potassium binder sodium zirconium cyclosilicate (Lokelma®) to treat inter-dialytic hyperkalemia will reduce the incidence and duration of post-dialysis atrial fibrillation.

Following screening, eligible subjects will undergo placement of an implantable cardiac loop recorder (LINQ device) to monitor for the development of atrial fibrillation or any clinically significant cardiac arrhythmias [CSCA]). After a two-week recovery period (to allow the patient to heal from cardiac loop recorder placement), patients will be randomized (1:1 ratio) to one of two treatment sequences:

- Sequence **A**: standard 2.0 K^+/2.5 Ca^{++} dialysate with no Lokelma supplementation for two (2) months, followed by a cross-over to experimental 3.0 K^+/2.5 Ca^{++} dialysate with Lokelma supplementation (on off-dialysis days) for two (2) months;

  Or

- Sequence **B**: experimental 3.0 K^+/2.5 Ca^{++} dialysate with Lokelma supplementation (on off-dialysis days) for two (2) months, followed by standard 2.0 K^+/2.5 Ca^{++} dialysate with no Lokelma supplementation for two (2) months.

  Each two-month treatment period (both 2.0 K^+/2.5 Ca^{++} dialysate and 3.0 K^+/2.5 Ca^{++} dialysate with Lokelma sequences) will be preceded by a two-week run-in period, to allow the patient to adapt to the new dialysate bath.

  While receiving the higher K+ dialysate, patient will be treated on off-dialysis days (4 days/week) with Lokelma, titrated to maintain K+ between 4.0 and 5.5 mEq/L. Refer to section 7.2 for the initial dose and frequency details.

Throughout both treatment phases, patients will undergo continuous cardiac monitoring using the programmable Medtronic Reveal LINQ ICM device to detect the development of atrial fibrillation or CSCA (i.e., pre-defined event of bradycardia, ventricular tachycardia, or asystole). The incidence of atrial fibrillation and CSCA events occurring during the two treatments (experimental vs standard) will be compared.

Study Objectives

Primary Efficacy Objective: Atrial Fibrillation Rates	**Primary Outcome Measure:**
To demonstrate whether increasing the K^+ concentration in a standard hemodialysis bath from 2.0 K^+/2.5 Ca^{++} to a 3.0 K^+/2.5 Ca^{++} composition with SZC will reduce the incidence of atrial fibrillation events [1].	➢ Frequency of atrial fibrillation events [1] occurring during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 dialysate cross-over periods.
Secondary Efficacy Objective #1: Clinically Significant Cardiac Arrhythmia Rates	**Secondary Outcome Measures:**
To determine whether the incidence and duration of post-dialysis CSCAs (defined as bradycardia, ventricular tachycardia and/or asystole [4]) observed during experimental treatment [2] will be reduced compared to standard treatment [3].	➢ Frequency of CSCAs (bradycardia, ventricular tachycardia and/or asystole) during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 dialysate cross-over periods. ➢ Total duration of CSCAs (bradycardia, ventricular tachycardia and/or asystole) during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 dialysate cross-over period.
Secondary Efficacy Objective #2: Events Outside the Optimal K^+ "Window"	**Secondary Outcome Measure:**
To determine whether the addition of oral sodium zirconium cyclosilicate (Lokelma®) during the 2-month treatment phase with the 3.0 K^+/2.5 Ca^{++} dialysate bath will reduce the risk of weeks outside the "K^+ safety range" of 4.0 to 5.5 mEq/L compared to the 2-month treatment phase with the 2.0 K^+/2.5 Ca^{++} dialysate bath.	➢ Whether or not K^+ outside of the 4.0 to 5.5 mEq/L safety range (a yes/no binary outcome). The risk of weekly events of pre-dialysis K^+ or the risk of post-dialysis K^+ falling outside the "K+ safety range" will be compared between the two dialysate groups.
Safety Objective #1: Lokelma Induced Hypokalemia	**Safety Outcome Measure:**
To evaluate whether the use of Lokelma during periods when patients are receiving a 3.0 K^+/2.5 Ca^{++} bath is associated with hypokalemic events defined as K^+ <3.5 mEq/L.	➢ Total number of hypokalemic events defined as Piccolo Point of Care Testing (POCT) or laboratory-measured K^+ of < 3.5 mEq/L.
Safety Objective #2: Incidence of Dialysis-related Hypokalemia, Hypomagnesemia, Hypophosphatemia, or Low Calcium	**Safety Outcome Measure:**

To determine the levels of K^+, Mg^{++}, calcium and PO_4 during dialysis (measured promptly prior to the termination of dialysis) during experimental treatment [2] compared to standard treatment [3]. Note: Each electrolyte is its own "safety" objective independently.	➢ Number of events (measured promptly prior to the termination of dialysis) where a Piccolo POCT measurement of K^+ is < 3.5 mEq/L OR Ca^{++} is < 7.0 mEq/L, OR Mg^{++} is < 2.0 mg/dl OR a PO_4 level is <3.0 mEq/L. All episodes where a specific electrolyte falls below the above listed threshold will be considered an "event" for that electrolyte. The total number of "events" will be recorded during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 cross-over periods.
Safety Objective #3: Adverse Experiences	**Safety Outcome Measure:**
To evaluate the safety and tolerability of the experimental treatment [2] compared to standard treatment [3] based on the frequency of reported adverse experiences.	➢ Frequencies of AEs, SAEs, and withdrawals due to AEs, with focus on treatment-related events.
Exploratory Objectives:	**Exploratory Outcome Measures:**
1) To evaluate the relationship between protein-bound uremic toxins (PBUTs) and atrial fibrillation rates. PBUTs such indoxyl sulfate (IS) and p-Cresol sulfate (PCS) can induce atrial fibrillation (*Aoki et al. 2015*; *Tang et al. 2015*).	➢ Correlation between PBUTs (IS, PCS, and ADMA) and the frequency of atrial fibrillation events.
2) To determine whether the levels of K^+, Mg^{++}, calcium and PO_4 (measured promptly prior to the termination of dialysis) correlate with the incidence of clinical events, including intradialytic hypotension, muscle cramping, and cardiac events (defined as atrial fibrillation, bradycardia, ventricular tachycardia, and asystole). We will also evaluate whether the 3.0 K^+ dialysate reduces the rates of these clinical events.	➢ Correlation between electrolyte levels and clinical events (intradialytic hypotension, muscle cramping, and cardiac events). ➢ Correlation between electrolytes falling below threshold levels (Ca^{++} < 7.0 mEq/L, PO_4 levels <3.0 mEq/L, Mg^{++}< 2.0 mg/dl, and K^+ of < 3.5 mEq/L) and cardiac events (defined as atrial fibrillation, bradycardia, ventricular tachycardia, or asystole).

Abbreviations: ADMA=asymmetric dimethylarginine; AE=adverse event; CSCA=clinically significant cardiac arrhythmia; IS=indoxyl sulfate; PBUT= protein-bound uremic toxin; PCS=p-Cresol sulfate; SAE=serious adverse event

[1] Atrial fibrillation will be defined as irregular heart rhythms and irregular R-R intervals in the absence of definable P waves for a minimum of 6 minutes. Each atrial fibrillation event will be adjudicated and validated as a true atrial fibrillation event by a central cardiologist who is blinded to dialysate K^+ content.

[2] Experimental treatment (8 weeks): hemodialysis using 3.0K^+/2.5 Ca^{++} dialysate bath, with sodium zirconium cyclosilicate (Lokelma®) supplementation on off-treatment days

[3] Standard treatment (8 weeks): hemodialysis using 2.0K^+/2.5 Ca^{++} dialysate bath, without sodium zirconium cyclosilicate (Lokelma®) supplementation

[4] CSCA events are defined as follows:

- Bradycardia: Heart rate of ≤ 40 beats per minute (BPM) for a minimum duration of 6 seconds.

- Ventricular Tachycardia: Regular tachy-arrhythmia of ≥ 130 BPM for a minimum duration of 30 seconds
- Asystole: Absence of detectable ventricular conduction for a minimum of 3 seconds

Target subject population

The ADAPT trial will enroll adult ESRD patients receiving hemodialysis for at least 3 months, who have shown reasonable compliance with dialysis sessions and medications, and had two (2) pre-dialysis K^+ measurements between 5.1 and 6.5 mEq/L following a long dialytic "weekend". Patients with a history of paroxysmal episodes of atrial fibrillation (excluding chronic atrial fibrillation) will be preferentially recruited. Patients with known left ventricular hypertrophy (LVH) and prior history of intra-dialytic cramping will also be identified, approached, and recruited for study participation.

Patient receiving peritoneal or home hemodialysis, or hemodialysis via a tunneled IVC catheter and with a known central stenosis of access extremity will be excluded from the study. Patients with the known placement of a dual or single chamber pacemaker or an automatic implantable cardiac defibrillator (AICD) will be ineligible for study participation.

Duration of treatment

Following the screening period's two confirmatory pre-dialysis K^+ measurements and after meeting study eligibility criteria, patients will be referred to the electrophysiology cardiologist of choice by the site principal investigator where a sub-cutaneous (SQ) continuous cardiac loop recorder will be placed in the left anterior chest wall. Patients will be allowed to accommodate to the loop recorder for 2-weeks before they are randomized (1:1 ratio) to one of two treatment sequences (Sequence A or B, as described above), and start study treatment with 2.0 K^+/2.5Ca^{++} dialysate bath without potassium binder supplementation or 3.0 K^+/2.5 Ca^{++} dialysate bath with Lokelma supplementation (taken on off-dialysis days). There will be a **2-week** cardiac monitoring blanking period where patients will be allowed to accommodate to the higher K^+ dialysate and the use of Lokelma. Any data recorded by the insertable loop recorder (ILR, LINQ device) during this time period will not be used for any endpoint analysis. During the next **8-week** treatment period (Phase I of the study), patients will undergo continuous cardiac monitoring by the ILR. At the end of Phase I, data will be downloaded from the ILR and a new **2-week** blanking period will begin where patients will "cross-over" to the alternative dialysate bath and will be allowed to equilibrate to the new dialysate. Patients dialyzed for 8 weeks using a 2.0 K^+/2.5Ca^{++} bath (without potassium binder supplementation) during Phase I will be switched to the 3.0 K^+/2.5 Ca^{++} bath with Lokelma supplementation, and *vice versa*. During the subsequent **8-week** treatment period (Phase II of the study), patients will undergo continuous cardiac monitoring by the ILR. At the conclusion of Phase II, a new cardiac monitoring blanking period will begin and blood sampling will be stopped. The ILR will be removed by the affiliated electrophysiology cardiologist. This process may take an additional 2 weeks. Therefore, for each patient, the planned total study treatment duration will be **20 weeks**, and the total study participation will be approximately **25 weeks**.

Investigational product, dosage, and mode of administration

The investigational product in this study is sodium zirconium cyclosilicate (Lokelma®), a potassium binder product for oral administration. Lokelma® for oral suspension will be supplied in 5.0 gram packets.

Patients will use Lokelma supplementation on off-dialysis days (4 days/week) while receiving hemodialysis with 3.0 K^+/2.5 Ca^{++} mEq dialysate bath. The individual starting dose will be 5.0 grams, and may be titrated weekly in 5.0 gram increments up to 15.0 grams to maintain K^+ between 4.0 and 5.5 mEq/L.

Statistical methods

Statistical Hypothesis

The primary statistical hypothesis of the study is that the rate of atrial fibrillation events during hemodialysis using the 3.0 K^+ dialysate bath supplemented with Lokelma is not equal to the rate of events incurred during hemodialysis using the 2.0 K^+ dialysate bath.

Sample Size Estimate

The sample size estimation is based upon the primary statistical hypothesis and its details are separately documented.

With >90% power to reject the primary hypothesis, 40 subjects would need to be randomized into one of two treatment sequences in the 2x2 cross-over study using the simulation study with a 2-sided alpha of 0.05, assuming an event rate of 4.6 with the 2.0 K^+ dialysate bath, an overdispersion parameter of 0.07 and a reduction of rate ratio of 25%. Accounting for an estimated 10% of randomized subjects not completing both study periods, **44 subjects** per treatment sequence or **88 subjects** in total will be randomized in the study.

Analysis Populations

- All-participants Analysis Set: will consist of all participants who were screened for the study.
- Full Analysis Set (FAS): will include all randomized patients, with patients being analyzed as randomized. All efficacy endpoints will be analyzed using the FAS.
- Safety Analysis Set (SAS): will include all randomized participants who during the first treatment period (study Phase I): (i) received at least one dose of the study drug (Lokelma) during treatment with the 3.0 K^+ dialysate bath; or (ii) completed Visit 2 during treatment with the 2.0 K^+ dialysate bath. All safety endpoints will be analyzed using the SAS.

Analysis of the Primary Variable

The primary efficacy endpoint is the frequency of atrial fibrillation events occurring during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 dialysate cross-over periods.

The primary analysis will test the null hypothesis that there is no difference in the rate of atrial fibrillation events between the 3.0K^+ dialysate bath with Lokelma and the 2.0K^+ dialysate bath without Lokelma, against the alternative hypothesis that there is a difference in the rate of atrial fibrillation events between the 3.0K^+ dialysate bath with Lokelma and the 2.0K^+ dialysate bath

without Lokelma. Statistical hypothesis testing will be completed at a 2-sided 0.05 significance level.

A generalized linear model assuming the distribution of negative binomial will be used, with fixed effect terms for the treatment groups ($3.0K^+$ dialysate bath with Lokelma and $2.0K^+$ dialysate bath without Lokelma), the study period, and log (the duration of period) as an offset variable. An independent working variance-covariance will be employed. Additional model terms may be included, details of which will be described in the SAP. The estimated risk ratio between groups and its 95% robust confidence interval (CI) will be displayed. The null hypothesis will be rejected if the p-value (based upon the Wald statistics) is less than 0.05.

The primary analysis will not account for missing values. However, sensitivity analyses will be conducted using the pattern mixture model with multiple imputation (PM-MI) method. Details of the PM-MI method will be provided in the SAP.

Interim Analysis

No interim analysis is planned.

Data Monitoring Committee

Not applicable.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADMA	asymmetric dimethylarginine
AE	adverse event
AICD	automatic implantable cardiac defibrillator
ALB	Albumin
BUN	Blood urea nitrogen
BPM	beats per minute
Ca^{++}	Calcium
CKD	chronic kidney disease
Cl^-	Chloride
CSCA	clinically significant cardiac arrhythmia
CSR	Clinical Study Report
CRE	Creatinine
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	deoxyribonucleic acid
DOPPS	Dialysis Outcomes and Practice Patterns Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EP	Electrophysiologist
ESRD	end-stage renal disease
FAS	Full Analysis Set
GCP	Good Clinical Practice
GLU	Glucose
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation

Abbreviation or special term	Explanation
ILR	insertable loop recorder
IP	Investigational Product
IS	indoxyl sulfate
IVRS	Interactive Voice Response System
IRT	Interactive Response Technology
K±	Potassium
LIDI	long inter-dialytic interval
LIMS	Laboratory information management system
LSLV	Last Subject Last Visit
LVH	left ventricular hypertrophy
MID	Monitoring in Dialysis (clinical trial acronym)
Mg^{++}	Magnesium
Na±	Sodium
NCI	National Cancer Institute
OAE	other significant adverse event
PBUT	protein-bound uremic toxin
PCR	polymerase chain reaction
PCS	p-Cresol sulfate
PHOS	Phosphorus
PI	Principal Investigator
POCT	Point of Care Testing
PWd	P-wave duration
RA	Research Agreement
RSI	Reference Safety Information – reference information for the expectedness of a serious adverse reaction to the IP
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCD	sudden cardiac death
SQ	Subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. INTRODUCTION

1.1 Background and Rationale for Conducting the Study

Patients with end-stage renal disease (ESRD) have significantly higher mortality rates compared to non-dialysis populations. Recent data from the United States Renal Data System (USRDS) database finds that the annualized death rates for all ESRD patients is approximately 23.7% with cardiac disease accounting for 40% of that number. Further analysis demonstrates that while the majority of ESRD patients have well defined risk factors for coronary disease, the cause of death is not due to atherosclerotic disease or myocardial infarction, but rather due to cardiac arrhythmias and sudden death. Moreover, these deaths parallel the weekly cycle of dialysis with the highest proportion occurring after the prolonged "dialysis weekend". This observation suggests that dialysis itself may directly contribute to the development of dysrhythmias presumably through the need to clear excess volume and electrolytes. The standard practice dialyzing patients with 2.0 mEq/L K^+ dialysate has been shown to slow atrial conduction rates and contribute to patient mortality. To further define the clinical risk factors that contribute to dialysis-associated arrhythmias, a growing number of studies have used continuous loop electrocardiogram (ECG) recorders which are subcutaneously implanted devices that have the capability for prolonged recordings of cardiac rhythms. These studies find that atrial fibrillation is the most common form of post-dialysis arrhythmia which can be observed in over 40% of dialysis patients for up to 12 hours after dialysis (*Roy-Chaudhury et al. 2018*). We propose that the use of a 3.0 mEq/L K^+ dialysate with the addition of Lokelma to control interdialytic hyperkalemia will reduce the rates of post-dialysis atrial fibrillation compared to dialysis with a standard 2.0 mEq/L K^+ dialysate.

1.1.1 Background and Significance

Atrial fibrillation is the most common cardiac arrhythmia affecting about 2% of those aged < 65 years and more than 9% among those over the age of 65 years or older in the United States (*Mozaffarian et al. 2016*). When compared to the general population, atrial fibrillation is even more prevalent with upwards to 20% of ESRD patients having been evaluated or treated for atrial fibrillation (*Soliman et al. 2010*). The increased incidence of atrial fibrillation is not limited to ESRD patients but has also been reported in patients with pre-dialysis chronic kidney disease (CKD). In a review of 62,459 patients with estimated glomerular filtration rate (eGFR) between 15-59 mL/min, Airy *et al* demonstrated that atrial fibrillation was present in up to 23% of patients with an all-cause mortality rate of 45% (*Airy et al. 2018*). These observations have led to the speculation that the actual delivery of dialysis contributes to the development of atrial fibrillation and other cardiac arrhythmias. To determine whether the electrolyte composition of dialysate was associated with the onset of cardiac sudden death, Pun and Middleton *et al* retrospectively performed a case-controlled analysis of over 17,000,000 dialysis sessions from the DaVita/Gambro database and examined the effect of dialysate potassium on sudden death rates. As shown in **Figure 1**, the incident rate of sudden cardiac arrhythmia was approximately 40% whether the patient was dialyzed with a low (<2.0 K^+) or standard (>2.0 K^+) dialysate. However, sudden death rates continued to climb up approximately 57% when the low K^+ dialysate was consistently used. In contrast, sudden death rates were the lowest among those patients whose pre-dialysis K^+ was 5.0. Even when the pre-dialysis K^+ was at 3.5 mEq/L, the

sudden death rate using a standard dialysate bath was approximately half the rate observed with low K^+ dialysates, while arrhythmia rates continued to climb with the low K^+ bath (*Pun et al. 2011*).

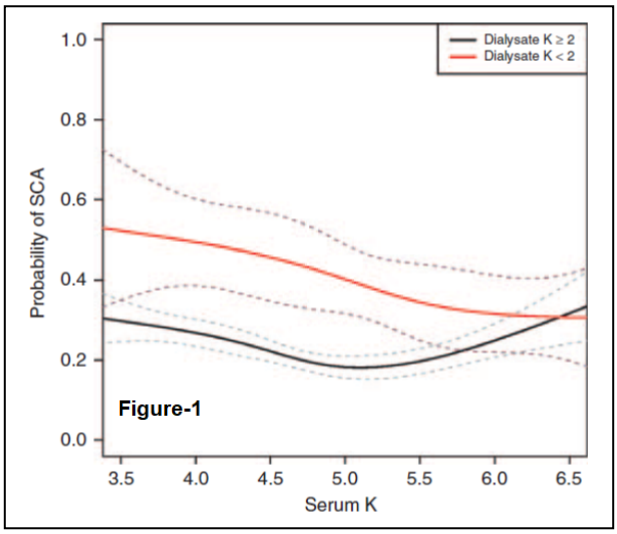


Figure 1 - Effect of Dialysate Potassium on the Incidence of Sudden Cardiac Arrhythmia

Source: *Pun et al. 2011*

This important paper suggests that a K^+ of 5.0 mEq/L may be optimal for preventing dialysis-associated arrhythmias. The observation that differences in dialysate K^+ levels markedly affected arrhythmia rates suggested that dialysis itself could be contributing to the markedly elevated sudden death rates among ESRD patients. To examine this question, Roy-Chaudhury and Tumlin et al. conducted the Monitoring in Dialysis (MID) Study in which 66 patients receiving outpatient hemodialysis underwent placement of the Reveal XT or Reveal LINQ (Medtronic, Minneapolis, MN) insertable cardiac monitoring device. This device allows for continuous and long-term detection of both atrial and ventricular arrhythmias before and after a dialysis for periods of up to 30 days. In this purely observational trial, participating patients were maintained on their standard dialysis prescription and the incident rates of atrial fibrillation, bradycardia, ventricular tachycardia, and asystole were monitored for 6 months. The study used a vigorous definition for atrial fibrillation requiring a minimum of a 6-minute duration to be considered clinically significant. As shown in **Figure 2**, 42% of patients experienced a clinically significant atrial fibrillation event during the 6 months of study. In addition, the rates of atrial fibrillation paralleled the "dialysis week", showing the highest rates during dialysis, but also showing significantly increased event rates for up to 12 hours after completion of a dialysis session. Moreover, when the investigators examined the difference in arrhythmia rates between patients being dialyzed with a 2.0 K^+ dialysate versus a 3.0 K^+ bath, there was a statistically lower rate of arrhythmias among patients dialyzed with the 3.0 K^+ bath ($P<0.0015$) (*Roy-Chaudhury et al. 2018*).

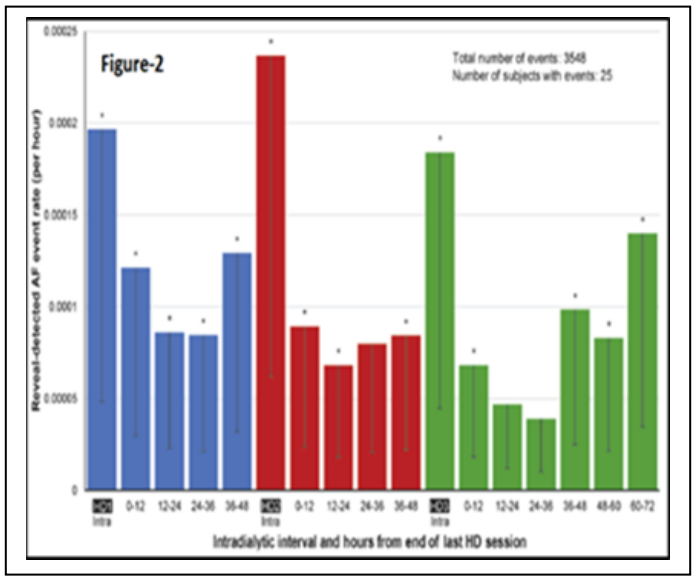


Figure 2 – Incidence of Clinically Significant Atrial Fibrillation in the MID Study

Source: *Roy-Chaudhury et al. 2018*

In a similar study, Sacher *et al* used an implantable loop recorder to extend the observations of Roy-Chaudry and Tumlin and determine clinical outcomes of patients with dialysis-associated arrhythmias. The incidence of specific arrhythmias was similar with 20% patients developing *de novo* atrial fibrillation or flutter with a nearly identical number developing bradycardia. Of the patients with bradycardia, 3 progressed to asystole and sudden death. An analysis of serum electrolytes at the time of the arrhythmia demonstrated that hyperkalemia was associated with conduction disorders while hypokalemia was associated with ventricular arrhythmias and atrial fibrillation (*Sacher et al. 2018*)**.** More recently, Ohnishi et.al conducted a cohort study of 3967 participants in the Dialysis Outcomes and Practice Patterns Study in Japan (DOPPS-Japan) and examined the long-term effects of post-dialysis hypokalemia on all-cause mortality and the incidence of cardiac mortality due to sudden death. As a part of the original observational protocol, participating patients had post-dialysis serum potassium (K^+) measured every 4 months. Patients were then divided into quartiles based upon the average post dialysis K^+. As can be seen in **Figure 3**, patients with low post-dialysis K+ (< 3.0 mEq/L) had significantly reduced survival with a hazard mortality of 1.89 (*Ohnishi et al. 2019*). These observations underscore the sensitivity of ESRD patients to electrolyte induced cardiac arrhythmia. Moreover, it points to the need to and the need to identify a "K+ safety range" and to individualize dialysate baths to achieve optimal before, after and during dialysis.

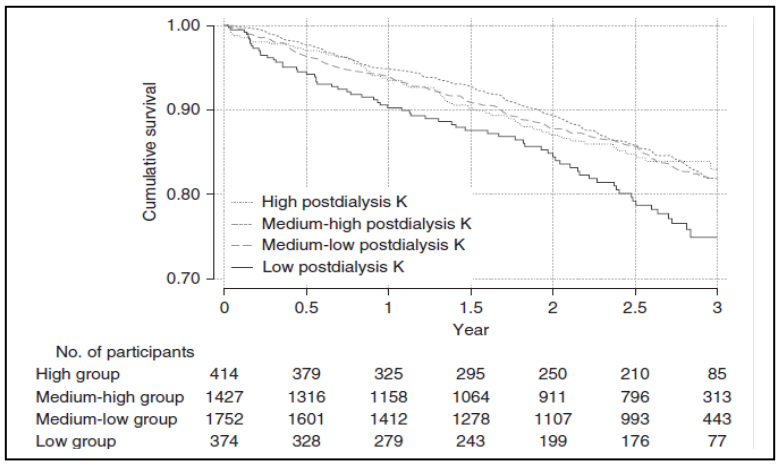


Figure 3 - Cumulative Survival by Post-dialysis K Group in the DOPPS-Japan Study

Low group: baseline post-dialysis K<3.0mEq/L; Medium-low group: baseline post-dialysis K≥3.0 to 3.5mEq/L; Medium-high group: post-dialysis K≥3.5 to 4.0 mEq/L; High group: post-dialysis K≥4.0 mEq/L.

Source: *Ohnishi et al. 2019*

The mechanisms by which K^+ changes during dialysis induce cardiac arrhythmias is unknown, but changes in P wave conductivity is a known risk factor for atrial fibrillation. Two recent studies that examined the effect of changes in post-dialysis K^+ have shown that P-wave duration (PWd) increased following dialysis, indicating a slowing in intra-atrial conduction velocity (see **Figure 4**). Moreover, the greater the change in K+ following dialysis correlates with an increase in P-wave velocity during a dialysis (*Severi et al. 2010*; *Krijthe et al. 2013*).

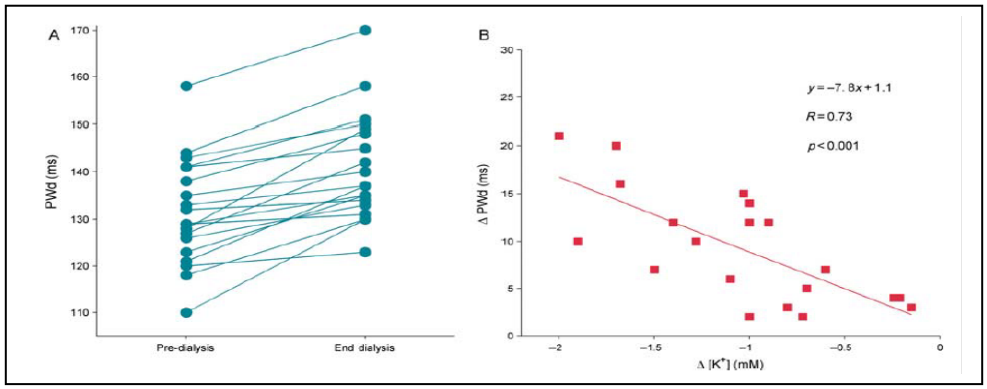


Figure 4 – (A) Haemodialysis-induced changes in P-wave duration. (B) Scatter plot and regression line showing the correlation between P-wave duration and serum K^+ concentration changes during haemodialysis sessions.

Source: *Severi et al. 2010*

Historically the K^+ concentration in a standard dialysate bath has been between 2.0 and 3.0 mEq/L, with the majority of dialysis sessions conducted with the 2.0 K^+ bath. Many of the studies high-lighted here have raised the question of whether the potassium concentration of the

"standard dialysate bath" should be re-assessed. The consistent and legitimate concern for such a change has been the development of hyperkalemia during the inter-dialytic period. The recent approval of novel and effective oral K^+ binders such at sodium zirconium cyclosilicate (Lokelma®) have provided a possible solution to the problem of inter-dialytic hyperkalemia. A recent study of 196 stable hemodialysis patients demonstrated that regular use of Lokelma on "off-dialysis days" is able to lower serum K^+ levels on interdialytic days. As shown in **Figure 5**, Lokelma was able to "optimize" pre-dialysis values to approximately 5.0 mEq/L (*Fishbane et al. 2019*). It is unclear whether this same effect could be accomplished using a higher (3.0 K^+) dialysate. We propose using Lokelma as a vehicle to allow for wide-spread use of higher dialysate baths which the hope that this maneuver would translate into lower rates of cardiac arrhythmias.

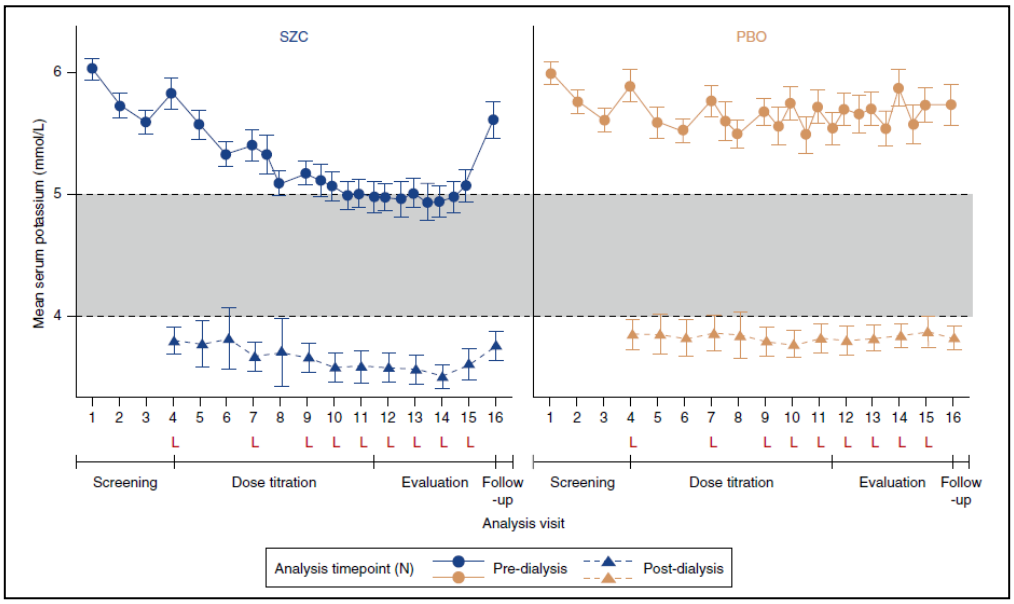


Figure 5 - Mean Pre- and Post-dialysis K+ values with SZC vs Placebo

Abbreviations: K=potassium; SZC=sodium zirconium cyclosilicate (Lokelma®)

Source: *Fishbane et al. 2019*

1.2 Rationale for Study Design, Doses, and Control Groups

Chronic outpatient hemodialysis patients have high rates of rapid changes in potassium and other electrolytes critical to the generation cardiac arrythmias. A growing body of data suggests that intra-dialytic K^+ levels fall to level of 2.0 or lower and are a potential major contributor to the generation of atrial fibrillation, bradycardia, and other clinically significant arrhythmias. We propose that raising the dialysate bath to 3.0 K^+ from current standard of care levels of 2.0 K^+ will reduce levels of hypokalemia-induced arrhythmias. We further propose that the use of sodium zirconium cyclosilicate (Lokelma®) will ensure that secondary hyperkalemia is controlled following the introduction of the 3.0 K^+ dialysate bath.

This is a prospective, open-labelled, cross-over design study of 88 patients with ESRD receiving routine outpatient dialysis using a standard 2.0K^+/2.5 Ca^{++} dialysate bath. NephroNet and the

study design team have chosen to use an open labelled design for the ADAPT trial due to the difficulty in attempting to "blind" a patient's dialysis solution. Moreover, due to the critical consequences of improper delivery of K^+ to ESRD patients, we considered it unethical to attempt a blinded study on safety grounds.

Patients will be monitored for the development of atrial fibrillation or clinically significant cardia arrhythmias (CSCA) using an implantable cardiac loop recorder (LINQ device). After 2 months of treatment, all enrolled patients will be "crossed-over" from either a 2.0 K^+ to a 3.0 K^+ dialysate bath or from a 3.0 K^+ to a 2.0 K^+ dialysate bath.

The study design also includes several measures aimed to minimize the risk of adverse experiences. Because patients with persistently high serum K^+ after the long dialysis weekend are not likely to tolerate the move to a higher K^+ dialysate, the enrollment criteria include a requirement for two (2) separate pre-dialysis measurements of serum K+ < 6.5 mEq/L. A two-week recovery period will allow patients to heal from cardiac loop recorder insertion before randomization. In addition, each two-month treatment period (both sequences) will be preceded by a two-week accommodation period, to allow the patient to adapt to the new dialysate bath. While receiving the higher K+ dialysate, patients will be treated on off-dialysis days (4 days/week) with oral Lokelma, to reduce interdialytic hyperkalemia. Lokelma will be titrated to maintain serum K+ levels within a safe range, between 4.0 and 5.5 mEq/L.

1.3 Benefit/risk and ethical assessment

End stage renal disease (ESRD) patients have significantly higher mortality rates compared to non-dialysis populations. Recent data from the USRDS database finds that the annualize death rates for all ESRD patients is approximately 23.7% with cardiac disease accounting for 40% of that number. Further analysis demonstrates that while the majority of ESRD patients have well defined risk factors for coronary disease, the cause of death is not due to atherosclerotic disease or myocardial infarction, but rather due to cardiac arrhythmias and sudden death. Current estimates indicate that up to 35% of deaths among chronic ESRD patients are due to sudden cardiac death (SCD). Any maneuvers to reduce dialysis-related arrythmias has the potential to significantly reduce the cardiovascular mortality among ESRD patients.

Potential benefits of study participation include:

1) Reduction in overall SCD rates

2) Potential for reduction in atrial fibrillation sequelae, including but not limited to embolic stroke, myocardial infarction, ischemic bowel disease, and acute critical limb ischemia

Potential risks associated with study participation include:

1) Excessive study treatment-associated hypokalemia, with potential exacerbation of arrhythmia
2) Risk for hypokalemia-associated muscle weakness, with risk for fall, etc.
3) Risk for local chest wall infection from insertion of the cardiac loop recorder device.

The discussion of risks and benefits to participating in the ADAPT trial and its goal of fine-tuning dialysate electrolyte composition highlights both the pressing need and difficulty of electrolyte management among ESRD populations. Based on available data (as presented in

Section 1.1) and the risk mitigation strategies incorporated in the study design, the benefit-risk assessment favours the initiation of the ADAPT trial.

1.4 Study Design

This is a prospective, open-labelled, randomized, 2x2 cross-over design study of 88 patients with end stage renal disease (ESRD) receiving routine out-patient dialysis using a standard 2.0 potassium ion (K^+)/2.5 calcium ion (Ca^{++}) dialysate bath. The overall aim of the study is to determine whether converting stable hemodialysis patients from a "standard" 2.0 K^+/2.5 Ca^{++} dialysate to a 3.0 K^+/2.5 Ca^{++} mEq dialysate supplemented with the orally administered potassium binder sodium zirconium cyclosilicate (Lokelma®) to treat inter-dialytic hyperkalemia will reduce the incidence and duration of post-dialysis atrial fibrillation.

Following the screening period's two confirmatory pre-dialysis K^+ measurements and after meeting study eligibility criteria, subjects will undergo placement of an implantable cardiac loop recorder (LINQ device) to monitor for the development of atrial fibrillation or any CSCA). After a two-week recovery period (to allow the patient to heal from the cardiac loop recorder placement), patients will be randomized (1:1 ratio) to one of two treatment sequences:

- Sequence **A**: standard 2.0 K^+/2.5 Ca^{++} dialysate with no Lokelma supplementation for two (2) months, followed by a cross-over to experimental 3.0 K^+/2.5 Ca^{++} dialysate with Lokelma (on off-dialysis days) for two (2) months;

  Or

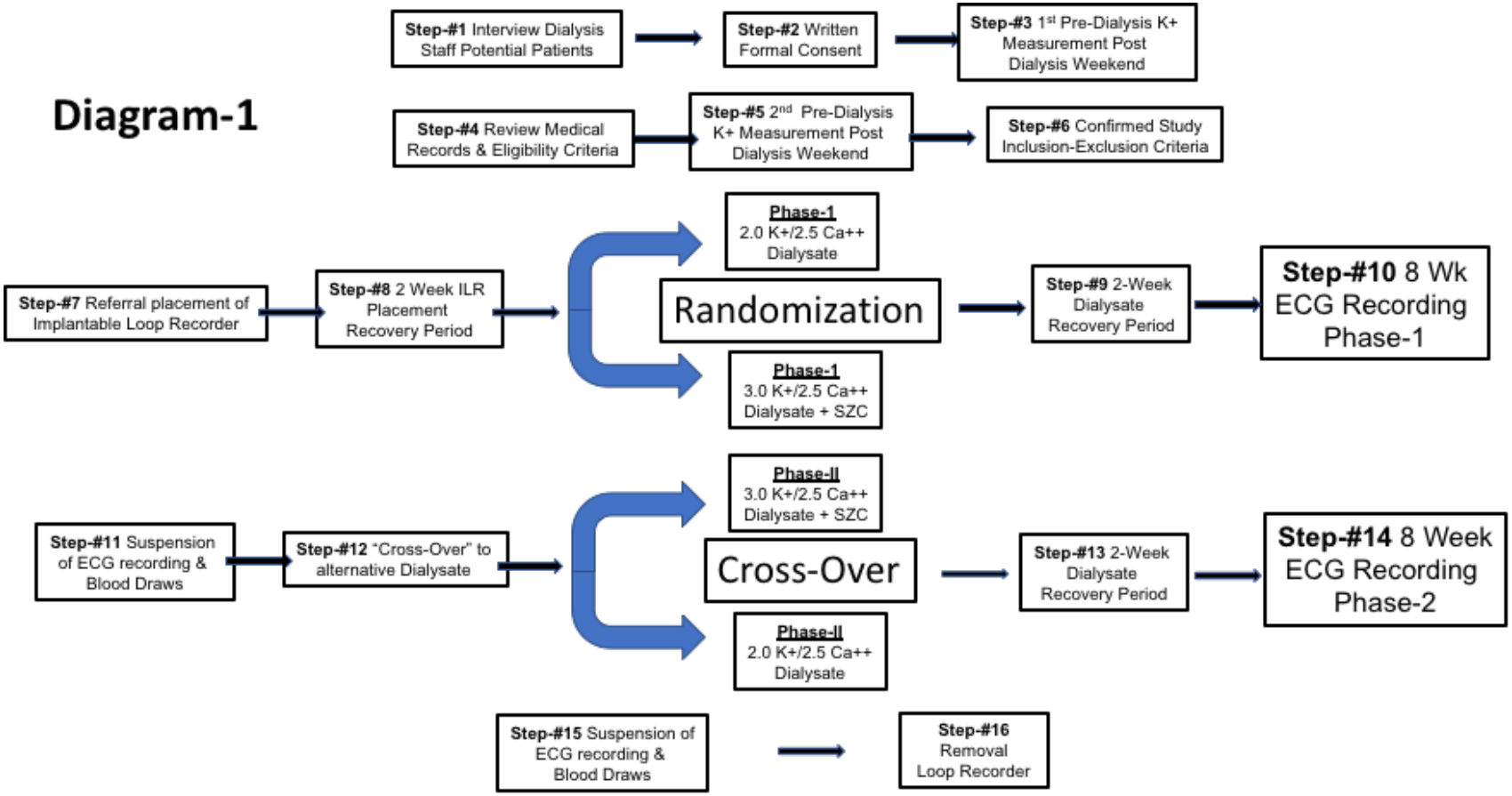
- Sequence **B**: experimental 3.0 K^+/2.5 Ca^{++} dialysate with Lokelma supplementation (on off-dialysis days) for two (2) months, followed by standard 2.0 K^+/2.5 Ca^{++} dialysate with no Lokelma supplementation for two (2) months.

  Each two-month treatment period (both 2.0 K^+/2.5 Ca^{++} dialysate and 3.0 K^+/2.5 Ca^{++} dialysate with Lokelma sequences) will be preceded by a two-week run-in period, to allow the patient to adapt to the new dialysate bath.

  While receiving the higher K^+ dialysate, patient will be treated on off-dialysis days (4 days/week) with Lokelma, titrated to maintain serum K^+ between 4.0 and 5.5 mEq/L.

Throughout both treatment phases, patients will undergo continuous cardiac monitoring using the programmable Medtronic Reveal LINQ ICM device to detect the development of atrial fibrillation or CSCA (i.e., pre-defined event of bradycardia, ventricular tachycardia, or asystole). The incidence of atrial fibrillation and CSCA events occurring during the two treatments (experimental vs standard) will be compared.

Figure 6 - Study Flow Chart



2. STUDY OBJECTIVES

2.1 Primary Objective

Primary Objective: Atrial Fibrillation Rates	Primary Outcome Measure:
To demonstrate whether increasing the K^+ concentration in a standard hemodialysis bath from 2.0 K^+/2.5 Ca^{++} to a 3.0 K^+/2.5 Ca^{++} composition with SZC will reduce the incidence of atrial fibrillation events. [1]	➢ Frequency of atrial fibrillation events [1] occurring during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 dialysate cross-over periods.

Abbreviations: CSCA=clinically significant cardiac arrhythmia

[1] Atrial fibrillation will be defined as irregular heart rhythms and irregular R-R intervals in the absence of definable P waves for a minimum of 6 minutes. Each atrial fibrillation event will be adjudicated and validated as a true atrial fibrillation event by a central cardiologist who is blinded to dialysate K^+ content.

[2] Experimental treatment (8 weeks): hemodialysis using 3.0K^+/2.5 Ca^{++} dialysate bath, with sodium zirconium cyclosilicate (Lokelma®) supplementation on off-treatment days

[3] Standard treatment (8 weeks): hemodialysis using 2.0K^+/2.5 Ca^{++} dialysate bath, without sodium zirconium cyclosilicate (Lokelma®) supplementation

2.2 Secondary Objectives

Secondary Efficacy Objective #1: Clinically Significant Cardiac Arrhythmia Rates	Secondary Outcome Measure:
To determine whether the incidence and duration of post-dialysis CSCAs (defined as bradycardia, ventricular tachycardia and/or asystole [1]) observed during experimental treatment [2] will be reduced compared to standard treatment. [3]	➢ Frequency of CSCAs (bradycardia, ventricular tachycardia and/or asystole) [1] occurring during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 dialysate cross-over periods. ➢ Total duration of CSCAs (bradycardia, ventricular tachycardia and/or asystole) [1] occurring during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 dialysate cross-over periods.
Secondary Efficacy Objective #2: Events Outside the Optimal K^+ "Window"	**Secondary Outcome Measure:**
To determine whether the addition of oral sodium zirconium cyclosilicate (Lokelma®) during the 2-month treatment phase with the 3.0 K^+/2.5 Ca^{++} dialysate bath will reduce risk of weeks outside the "K^+ safety range" of 4.0 to 5.5 mEq/L compared to the 2-month treatment phase with the 2.0 K^+/2.5 Ca^{++} dialysate bath.	➢ Whether or not K^+ outside of the 4.0 to 5.5 mEq/L safety range (Yes/No binary outcome measure). The risk of weekly events of pre- dialysis K^+ or the risk of post-dialysis K^+ falling outside the "K+ safety range" will be compared between the two dialysate groups.

Abbreviations: CSCA=clinically significant cardiac arrhythmia

[1] CSCA events are defined as follows:

- Bradycardia: Heart rate of ≤ 40 beats per minute (BPM) for a minimum duration of 6 seconds.
- Ventricular Tachycardia: Regular tachy-arrhythmia of ≥ 130 BPM for a minimum duration of 30 seconds
- Asystole: Absence of detectable ventricular conduction for a minimum of 3 seconds

[2] Experimental treatment (8 weeks): hemodialysis using 3.0K^+/2.5 Ca^{++} dialysate bath, with sodium zirconium cyclosilicate (Lokelma®) supplementation on off-treatment days

[3] Standard treatment (8 weeks): hemodialysis using 2.0K^+/2.5 Ca^{++} dialysate bath, without sodium zirconium cyclosilicate (Lokelma®) supplementation

2.3 Safety Objectives

Safety Objective #1: Lokelma-Induced Hypokalemia	**Safety Outcome Measure:**
To evaluate whether the use of oral sodium zirconium cyclosilicate (Lokelma®) during periods when patients are receiving a 3.0 K^+/2.5 Ca^{++} dialysate bath is associated with hypokalemic events defined as K^+ <3.5 mEq/L.	➢ Total number of hypokalemic events defined as Piccolo POCT or laboratory-measured K^+ of < 3.5 mEq/L.
Safety Objective #2: Incidence of Dialysis-related Hypokalemia, Hypomagnesemia, Hypophosphatemia, or Low Calcium	**Safety Outcome Measure:**
To determine the levels of K^+, Mg^{++}, calcium and PO_4 during dialysis (measured promptly prior to the termination of dialysis) during experimental treatment [2] compared to standard treatment [3]. Note: Each electrolyte is its own "safety" objective independently.	➢ Number of events (measured promptly prior to the termination of dialysis) where a Piccolo POCT measurement of K^+ is < 3.5 mEq/L OR Ca^{++} is < 7.0 mEq/L, OR Mg^{++} is < 2.0 mg/dl, OR a PO_4 level is <3.0 mEq/L. All episodes where a specific electrolyte falls below the above listed threshold will be considered an "event" for that electrolyte. The total number of "events" will be recorded during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 cross-over periods.
Safety Objective #3: Adverse Experiences	**Safety Outcome Measure:**
To evaluate the safety and tolerability of the experimental treatment [2] compared to standard treatment [3] based on the frequency of reported adverse experiences.	➢ Frequencies of AEs, SAEs, and withdrawals due to AEs, with focus on treatment-related events.

Abbreviations: AE=adverse event; CSCA=clinically significant cardiac arrhythmia; SAE=serious adverse event

[2] Experimental treatment (8 weeks): hemodialysis using 3.0K^+/2.5 Ca^{++} dialysate bath, with sodium zirconium cyclosilicate (Lokelma®) supplementation on off-treatment days

[3] Standard treatment (8 weeks): hemodialysis using 2.0K^+/2.5 Ca^{++} dialysate bath, without sodium zirconium cyclosilicate (Lokelma®) supplementation

2.4 Exploratory Objectives

Exploratory Objectives:	Outcome Measures:
1) To evaluate the relationship between protein-bound uremic toxins (PBUTs) and atrial fibrillation rates. PBUTs such indoxyl sulfate (IS) and p-Cresol sulfate (PCS) can induce atrial fibrillation (*Aoki et al. 2015*; *Tang et al. 2015*).	➢ Correlation between PBUTs (IS, PCS, and ADMA) and the frequency of atrial fibrillation events.
2) To determine whether the levels of K^+, Mg^{++}, calcium and PO_4 (measured promptly prior to the termination of dialysis) correlate with the incidence of clinical events, including intradialytic hypotension, muscle cramping, and cardiac events (defined as atrial fibrillation, bradycardia, ventricular tachycardia, and asystole). We will also evaluate whether the 3.0 K^+ dialysate reduces the rates of these clinical events.	➢ Correlation between electrolyte levels and clinical events (intradialytic hypotension, muscle cramping, and cardiac events). ➢ Correlation between electrolytes falling below threshold levels (Ca^{++} < 7.0 mEq/L, PO_4 levels <3.0 mEq/L, Mg^{++}< 2.0 mg/dl, and K^+ of < 3.5 mEq/L) and cardiac events (defined as atrial fibrillation, bradycardia, ventricular tachycardia, and asystole).

Abbreviations: ADMA=asymmetric dimethylarginine; IS=indoxyl sulfate; PBUT=protein-bound uremic toxin; PCS= p-Cresol sulfate

3. SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

All study participants will be recruited from specialist (nephrology) care clinics.

Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion Criteria

For inclusion in the study subjects should fulfil the following criteria based on local regulations:

1. Provision of informed consent prior to any study-specific procedures
2. Female or male aged above 18 years
3. Patients with ESRD receiving hemodialysis three times per week for a minimum of 3 months
4. Patients must have two (2) pre-dialysis K^+ measurements between 5.1 and 6.5 mEq/L by Piccolo POCT following the long dialytic “weekends” (i.e., on two consecutive Mondays for patients on a Monday-Wednesday-Friday dialysis schedule or on two consecutive Tuesdays for patients on a Tuesday-Thursday-Saturday dialysis schedule) during screening, before insertion of the cardiac loop recorder.
5. Female participants must be 1 year post-menopausal, surgically sterile, or using one highly effective form of birth control (defined as one that can achieve a failure rate

of less than 1% per year when used consistently and correctly.) They should have been stable on their chosen method of birth control for a minimum of 1 month before entering the study and willing to remain on the birth control until 4 weeks after the last dose.

3.2 Exclusion Criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

Exclusion Criteria Related to the Underlying Condition:

1. Patients with a QTc(f) > 550 msec and/or Congenital long QT syndrome
2. Patients with a Haemoglobin < 9 g/dl.
3. Patients with any medical condition, including active, clinically significant infection or liver disease, that in the opinion of the investigator or Sponsor may pose a safety risk to a subject in this study, which may confound safety or efficacy assessment and jeopardize the quality of the data, or may interfere with study participation.
4. Patient receiving peritoneal or home hemodialysis
5. Patient receiving hemodialysis via a tunneled inferior vena cava (IVC) catheter and known central stenosis of access extremity
6. Patient receiving outpatient hemodialysis for < 3 months
7. Patient receiving outpatient hemodialysis for prolonged Acute Kidney Injury (AKI) and considered by the site Principal Investigator (PI) likely to achieve renal recovery within 6 months

   Note: Patients receiving out-patient hemodialysis for AKI for longer than 6 months with no demonstrable renal clearance can be screened for study participation.
8. Patient currently receiving a 1.0 K^+, 3.0 K^+ dialysate bath and unwilling to convert to a 2.0 K^+/2.5 Ca^{++} dialysate bath
9. Subject unwilling to convert from a 2.0 K^+ dialysate bath to a 3.0 K^+ dialysate bath
10. Two or more pre-dialysis K^+ of < 5.1 or > 6.5 mEq/L measured by Piccolo POCT after the long dialytic "weekends" during screening

    Note: If one of the two screening pre-dialysis K+ levels is between 4.6 to 5.0 mEq/L or 6.6 to 7.0 mEq/L, the patient can undergo an additional whole blood Piccolo POCT K^+ measurement. Patients who fail the third whole blood Piccolo POCT K^+ measurement will be considered ineligible for study participation. Note: Screen failures can be re-screened once to confirm eligibility in the study.
11. Any documented whole blood Piccolo POCT K^+ measurement that falls below 4.6 mEq/L or exceeds 7.0 mEq/l during the screening period
12. Current use of a medication for treatment of hyperkalemia (e.g., Patiromer).

Note: If a medication for treatment of hyperkalemia is stopped prior to or after the consenting process, the subject will undergo a one week washout prior to the first whole blood Piccolo POCT K^+ measurement.

Exclusion Criteria Related to Other Medical Conditions and Treatments:

13. Anticipated life expectancy of <6 months, as assessed by the site PI
14. Chronic atrial fibrillation, defined as sustained atrial fibrillation of >3 months duration
15. Development of atrial fibrillation requiring hospitalization, medical therapy, anticoagulation, or cardioversion during study pre-screening or screening period
16. Patient with a known placement of a dual or single chamber pacemaker
17. Patient with an automatic implantable cardiac defibrillator (AICD)
18. Patient with a LINQ implanted cardiac loop recorder with less than 6 months of battery life.
19. Current use of amiodarone or other anti-arrhythmic therapy.

    Note: Patients on such medications must undergo a two week washout prior to the first whole blood Piccolo POCT K+ measurement.
20. Known history of cardiac arrhythmias due to prolonged QT syndrome
21. Subject unwilling to receive an implanted LINQ cardiac loop recorder (unless 6 months are remaining in their previously implanted device).
22. Known active drug abuse
23. Positive hepatitis C polymerase chain reaction (PCR) test with active viral deoxyribonucleic acid (DNA) shedding or chronic active hepatitis B as evidenced by detectable surface antigen from standard of care routine dialysis labs.

    Note: Patients with negative PCR DNA testing for either hepatitis B or C will be allowed to participate in the study.
24. Known to have tested positive for human immunodeficiency virus (HIV) from standard of care routine dialysis labs.
25. For women only: currently pregnant (confirmed with positive pregnancy test) or breastfeeding.
26. Patients with known and/or active severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders or diabetic gastroparesis

Exclusion Criteria Related to the Investigational Product (IP):

27. Known hypersensitivity to sodium zirconium cyclosilicate (Lokelma®).

Other/General Exclusion Criteria:

28. Previous randomization in the present study. Note: Screen failures can be re-screened once to confirm eligibility in the study.

29. Participation in another interventional (non-observational) clinical study within 4 weeks prior to enrollment in the present study

Procedures for withdrawal of incorrectly enrolled subjects are provided in Section 3.4.

3.3 Subject Enrollment and Randomization

Study participants will be recruited from each site's current and actively managed dialysis population. ESRD patients on a three times weekly hemodialysis regimen will be identified through regular monthly rounding visits by the site PI / Delegated Staff and through interactions with the dialysis unit nursing staff. Patients with a known history of dialysis-associated atrial fibrillation will be sought out for participation in the study. Site PIs will attempt to enroll at least 25% of their patients with a known history of post-dialysis intermittent (but not chronic) atrial fibrillation. Prospective patients will be approached by the site PI or designated clinical research staff to obtain written informed consent before any study-specific screening procedures commence. A log of all patients who entered pre-study screening will be maintained by the site research team.

Patients who meet all inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to one of two treatment sequences, consistent with a two-period cross-over design. Central randomization via an interactive response technology (IRT) will be utilized; refer to Section 3.5 for details. Randomization codes will be assigned strictly sequentially as patients become eligible for randomization.

A total of 88 patients are planned to be randomized, accounting for an anticipated 10% drop-out rate. Patients who discontinue or are withdrawn from the study post-randomization WILL NOT be replaced (i.e., their randomization code cannot be reused).

3.4 Procedures for Handling Incorrectly Enrolled or Randomized Subjects

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the PI should inform the Sponsor immediately, and a discussion should occur between the Sponsor and the PI regarding whether to continue or discontinue the patient from treatment. The Sponsor must ensure all decisions are appropriately documented.

3.5 Methods for Assigning Treatment Groups

The study sponsor (NephroNet) will be responsible for preparing the randomization scheme. Permuted block randomization using 2x2 Latin Squares will be applied to ensure a balanced assignment (1:1 ratio) to the two treatment sequences in the study.

Patients who meet all inclusion and none of the exclusion criteria will be randomized to one of two treatment sequences, consistent with a two-period cross-over design:

- Sequence **A**: standard 2.0 K^+/2.5 Ca^{++} dialysate with no Lokelma supplementation for two (2) months, followed by a cross-over to experimental 3.0 K^+/2.5 Ca^{++} dialysate with Lokelma supplementation (on off-dialysis days) for two (2) months;

  Or

- Sequence **B**: experimental 3.0 K^+/2.5 Ca^{++} dialysate with Lokelma supplementation (on off-dialysis days) for two (2) months, followed by standard 2.0 K^+/2.5 Ca^{++} dialysate with no Lokelma supplementation for two (2) months.

Central randomization via an interactive response technology (IRT) will be utilized. Randomization codes will be assigned strictly sequentially as patients become eligible for randomization. Randomization will occur by the site PI (or qualified designee) contacting the IRT and obtaining the randomization code and associated treatment sequence for each eligible patient. The original randomization notification will be filed as part of the source documents.

Sites are expected to randomize approximately nine (9) patients on average (no minimum or maximum number of enrolled patients will be specified).

3.6 Methods for ensuring blinding

Not applicable; this is an open label study.

3.7 Methods for unblinding

Not applicable; this is an open label study.

3.8 Restrictions

Apart from the limitations described in the exclusion criteria (see Section 3.2), there will be no restrictions affecting patients' daily life activities associated with participation in the study.

3.9 Discontinuation of Investigational Product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment;
- Incorrectly randomized participant where violation of the inclusion/exclusion criteria would put the participant at undue risk;
- Adverse event for which the investigator judges continued treatment may put the participant at undue risk;
- Pregnancy;
- Development of any of the following study-specific criteria for discontinuation:
  - Permanent atrial fibrillation, as determined by echocardiogram or cardiology assessment;

- Requiring for permanent placement of a cardiac pacemaker or AICD;
- Refractory hyperkalemia (K^+ > 6.5 mEq/L) while on 15 grams 4 days per week of Lokelma;
- Hypokalemic event (defined as pre-dialysis K+ level of < 3.5 mEq/L): Patients experiencing a minimum of two (2) hypokalemic events while taking Lokelma will have their Lokelma adjusted or discontinued at the discretion of the site PI;
- Renal transplant.

- Severe non-compliance with the study protocol.

Note: patients wishing to remain in the study on treatment despite developing an adverse event may do so at the site PI's discretion, unless they remain hyperkalemic with K^+ > 6.5 mEq/L after a long inter-dialytic interval (LIDI) for two (2) consecutive weeks.

Regardless of the reason for discontinuation, all reasons for discontinuation of study treatment must be documented in the electronic case report form (eCRF).

If the patient is discontinued from investigational product, the scheduled study visits, data collection and procedures should continue according to the study protocol until study completion, unless the patient withdraws consent for any further study procedures and follow-up. The approach taken should be documented in the eCRF.

3.9.1 Procedures for Discontinuation of a Patient from Investigational Product

At any time, patients are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.10), without prejudice to further treatment. Patients deciding to discontinue the investigational product will be asked to: (i) provide the reason(s) for discontinuation, including the development of any adverse event(s) contributing to their decision; (ii) return to the clinic for the remaining study visit(s) and assessment(s); and (iii) return all unused study drug to the site. Adverse events will be followed up, as described in Section 6.

The investigational product (Lokelma) can be discontinued abruptly (without the need for gradual treatment stepdown or tapering). Patients may be allowed to re-start the investigational product at the discretion of the site PI.

Patient withdrawal from study is described in Section 3.10.

3.10 Criteria for Withdrawal

Patients can decide to be discontinued from both investigational product **and** further study procedures/visits at any time (withdrawal of consent).

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrollment' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. Regardless of the reason for withdrawal, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF.

If a patient withdraws from participation in the study, his/her randomization code cannot be reused. Withdrawn randomized patients will not be replaced.

Patients who withdraw consent prior to completion of the study, will have the option to either keep the ILR device implanted or have their ILR device removed by the affiliated electrophysiology cardiologist.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of the Sponsor, trial participants are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug
- are not considered to be consistent with continuation of the study.
- Unscheduled ECG will be performed if a patient develops a suspected arrhythmia since date from the loop recorded will not be evaluated simultaneously. ECG will also be measured if S-K < 3.0. If an absolute QTc >550ms, or an increase in QTc interval > 60ms from baseline to more than 500ms is reached the subject will immediately receive appropriate medical intervention and be discontinued from the study drug treatment. The QTcF algorithm (QT interval corrected by the Fridericia method) is recommended. All patients meeting the QTc>500ms criterion will immediately have potassium assessed, if not already done within 1 hour of performing the ECG.

Regardless of the reason for termination, all participant data available at the time of study stopping must be recorded in the eCRF. For patients still in the study at the time of study discontinuation, the reasons for discontinuation should be documented as “Study termination by the Sponsor”.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients’ interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

The Study Plan and schedule of assessments is provided in Table 1.

Details of study assessments completed during the Screening, Treatment, and Follow-up periods are included in sections 4.1, 4.2, and 4.3.

Table 1 Study Plan and Schedule of Assessments

Study Period / Visit	Screening	ILR Insertion by EP cardiologist	Baseline/ Randomization	New Dialysate Accommo-dation Period 1	Treatment Phase 1	Cross-over	New Dialysate Accommo-dation Period 2	Treatment Phase 2	ILR Removal by EP cardiologist	End of Study	Reference to Protocol Section
Study Week (Wk) [* , ** or *]**	**-4 to -3****	**-2***	**1****	**1 & 2****	**3 to 10****	**11****	**11 & 12****	**13 to20****	**21-22***	**22-23*****	
Study Day (D)	**-28 to -15**	**-14**	**1**	**1 to 14**	**15 to 70**	**71**	**71 to 84**	**85 to 140**	**Between D141 and D155**	**Within 1 to 14 days after ILR Removal**	
Day of the week			M/T	M/T	M/T	M/T	M/T	M/T			
Written informed consent	X										4.1.1
Assignment of unique Screening Number	X										4.1.2
Demographics	X										4.1.3
Medical/surgical & Medication history	X										4.1.4
Physical examination	X										4.1.5
Vital signs and weight measurements	X			X	X		X	X		X	4.1.6
12-lead ECG	X										5.2.3.1
K+ Piccolo POCT (pre-dialysis) [1]	X			X	X		X	X			4.1.7 4.2.1

Table 1 Study Plan and Schedule of Assessments

Study Period / Visit	Screening	ILR Insertion by EP cardiologist	Baseline/ Randomization	New Dialysate Accommo-dation Period 1	Treatment Phase 1	Cross-over	New Dialysate Accommo-dation Period 2	Treatment Phase 2	ILR Removal by EP cardiologist	End of Study	Reference to Protocol Section
Study Week (Wk) [* , ** or *]**	**-4 to -3****	**-2***	**1****	**1 & 2****	**3 to 10****	**11****	**11 & 12****	**13 to20****	**21-22***	**22-23*****	
Study Day (D)	**-28 to -15**	**-14**	**1**	**1 to 14**	**15 to 70**	**71**	**71 to 84**	**85 to 140**	**Between D141 and D155**	**Within 1 to 14 days after ILR Removal**	
Inclusion/exclusion criteria	X		X								3.1, 3.2
Day of the Week			M/T	M/T	M/T	M/T	M/T	M/T			
ILR insertion [7]		X									4.1.9
Randomization to one of two treatment sequences [6]			X								3.5
Study drug dispensed/ returned on 3.0 K+/2.5 Ca++ dialysate group				X	X		X	X			7.2.2
Cardiac Data Loop Recordings					X			X			4.2.2
K+, Ca++ and PO_4 Piccolo POCT promptly before dialysis end) [2]				X	X		X	X			4.2.1

Table 1 Study Plan and Schedule of Assessments

Study Period / Visit	Screening	ILR Insertion by EP cardiologist	Baseline/ Randomization	New Dialysate Accommo-dation Period 1	Treatment Phase 1	Cross-over	New Dialysate Accommo-dation Period 2	Treatment Phase 2	ILR Removal by EP cardiologist	End of Study	Reference to Protocol Section
Study Week (Wk) [* , ** or *]**	**-4 to -3****	**-2***	**1****	**1 & 2****	**3 to 10****	**11****	**11 & 12****	**13 to20****	**21-22***	**22-23*****	
Study Day (D)	**-28 to -15**	**-14**	**1**	**1 to 14**	**15 to 70**	**71**	**71 to 84**	**85 to 140**	**Between D141 and D155**	**Within 1 to 14 days after ILR Removal**	
Blood samples for PBUTs [3]					X						4.2.1
Day of the Week			M/T	M/T	M/T	M/T	M/T	M/T			
Local laboratory Mg^{++} promptly before dialysis end) [4]				X	X		X	X			4.2.1
Adverse event recording & review [8]				X	X	X	X	X	X	X	6.4
Serious Adverse event recording & review [9]	X	X	X	X	X	X	X	X	X	X	6.4
Concomitant medication	X	X	X	X	X	X	X	X	X	X	5.2.5, 7.7
Local laboratory Mg^{++} promptly before dialysis end) for muscle cramping [5]				X	X		X	X			4.2.1

Table 1 Study Plan and Schedule of Assessments

Study Period / Visit	Screening	ILR Insertion by EP cardiologist	Baseline/ Randomization	New Dialysate Accommo-dation Period 1	Treatment Phase 1	Cross-over	New Dialysate Accommo-dation Period 2	Treatment Phase 2	ILR Removal by EP cardiologist	End of Study	Reference to Protocol Section
Study Week (Wk) [* , ** or *]**	**-4 to -3****	**-2***	**1****	**1 & 2****	**3 to 10****	**11****	**11 & 12****	**13 to20****	**21-22***	**22-23*****	
Study Day (D)	**-28 to -15**	**-14**	**1**	**1 to 14**	**15 to 70**	**71**	**71 to 84**	**85 to 140**	**Between D141 and D155**	**Within 1 to 14 days after ILR Removal**	
Pregnancy Test for Females of Childbearing Potential	X										4.1.4. 5.2.6

Abbreviations: AE=adverse event; Ca=calcium; ECG=electrocardiogram; EP=electrophysiologist; ILR=insertable loop recorder; K=potassium; Mg^{++}=magnesium; PBUTs=protein-bound uremic toxins [including p-Cresol sulfate [PCS], indoxyl sulfate, and asymmetric dimethylarginine [ADMA]); SAE=serious adverse event

*Performed on any day. (Note: ILR placement needs to be one week prior to baseline, which starts on Mondays or Tuesdays after each long dialysis weekend.)

**Performed weekly, on Mondays or Tuesdays after each long dialysis weekend. (Note: Screening ICF can be obtained on any dialysis day, but all other procedures need to be performed on Monday or Tuesdays after the long dialysis weekend. Additionally, consenting may be conducted several weeks prior to other study procedures depending on the need for a prohibited medication washout or whether the consenting process occurred on a day other than the Monday or Tuesday after the long dialysis weekend.)

***Performed on any dialysis day

[1] K^+ Piccolo POCT (utilizing full renal panel) are performed pre-dialysis, on a Monday or Tuesday after the long dialysis weekend, twice during the Screening period, and weekly during the treatment period (both 2-week accommodation periods and 8-week Treatment phases). Note: K^+ Piccolo POCT may be performed several weeks after consenting depending on the need for a prohibited medication washout or whether the consenting process occurred on a day other than the Monday or Tuesday after the long dialysis weekend.

[2] During the treatment period (both 2-week accommodation periods and 8-week Treatment phases), a second Piccolo POCT is performed promptly before dialysis end and within 30 minutes prior to rinse back on Mondays or Tuesdays after each long dialysis weekend (i.e., weekly), to measure K^+ ,Ca++and PO_4.

[3] Applies only to the first twenty-five (25) patients randomized receiving standard treatment (hemodialysis using 2.0K+/2.5 Ca++ dialysate bath, without Lokelma supplementation) during Treatment Phase-1. Performed weekly, on Mondays or Tuesdays after each long dialysis weekend, promptly before dialysis end and within 30 minutes prior to rinse back.

[4] Performed weekly, on Mondays or Tuesdays after each long dialysis weekend, promptly before dialysis end and within 30 minutes prior to rinse back. Mg^{++} levels will be determined by the local laboratory at each site.

[5] Performed (if possible) upon symptomatic muscle cramping, promptly before dialysis end and within 30 minutes prior to rinse back. Mg^{++} levels will be determined by the local laboratory at each site.

[6] Baseline/Randomization is conducted on Week 1 of the new Dialysate Accommodation Period 1. Crossover occurs on the same day as Week 11 of the new Dialysate Accommodate Period 2. Neither Baseline/Randomization nor Crossover will be considered a separate visit.

[7] If ILR insertion is performed more than 30 days after the last K^+ Piccolo POCT determination, please contact the sponsor who will determine if an additional K^+ Piccolo POCT determination will be required prior to the baseline visit. These will be handled on a case-by-case basis.

[8] Adverse events will be collected from the time of first dose of Lokelma[â], throughout the treatment and post-treatment follow-up period, up to the last study visit.

[9] SAEs will be reported from the time the patient signed the Informed Consent Form.

4.1 Screening Period

The process for identifying prospective study patients (pre-screening) is described in Section 3.3.

Screening assessments will be carried out according to the schedule provided in **Table 1**. The following section details the screening activities, starting with the consent process. During screening, consenting patients will be assessed to ensure that they meet all eligibility criteria. Patients who do not meet these criteria must not be randomized in the study.

4.1.1 Obtaining Written Informed Consent

Potential patients expressing a willingness to participate in the study will be interviewed by the Site PI or their qualified designee, and the study objectives, benefits and risks of participation, and study requirements will be thoroughly reviewed with the patient. The patient will be given a copy of the consent form to review, and adequate time will be provided to ask questions, discuss with family members, and decide about study participation. If the patient wishes to participate in the study, he/she will be required to provide written informed consent prior to any study-specific procedures commence. A copy of the signed consent form will be given to the patient and the original will be kept in the patient file with the source documents.

Note: Consenting may be conducted several weeks prior to other study procedures depending on the need for a prohibited medication washout or whether the consenting process occurred on a day other than the Monday or Tuesday after the long dialysis weekend.

4.1.2 Assignment of Unique Patient Enrollment Number

Consenting patients will be assigned a unique Patient Enrollment Number comprised by a 2-digit site number, and a sequentially assigned 3-digit number starting with 001. For example, at site 01, the first enrolled patient will be assigned 01-001, the second patient 01-002, etc. If the second patient does not meet all the inclusion/exclusion criteria (e.g., the patient fails to meet the required K^+ ranges), his/her Patient Enrollment Number will not be replaced, and the 3rd consenting patient will be assigned 01-003.

Upon randomization, the patients will be assigned a sequential subject number of 01 through 88.

4.1.3 Recording of Demographic Data

Demographic data (date of birth, sex, self-reported race, and ethnicity) will be recorded at screening.

4.1.4 Review of Medical/Surgical, Laboratory, and Medication History

Patient medical records and prior dialysis flow sheets will be reviewed to determine whether the patient meets all inclusion and none of the exclusion criteria. The review will include, but will not be limited to the following:

1) Routine "standard of care" laboratory data for the 2 months prior to giving written informed consent.

2) Routine "standard of care" determinations of the ratio of urea clearance (K) multiplied by dialysis time (t) to the volume of water in the body (Kt/V) for the 2 months prior to giving written informed consent.
3) Routine dialysis parameters, such as blood flow (Qb), dialysate flow (Qd), amount of fluid ultra-filtrated during dialysis (Delta UF) and post-dialysis exit weight for each of the 2 months prior to giving written informed consent.
4) Evidence of past history of intermittent atrial fibrillation (patients with > 3 months of continuous atrial fibrillation will be considered ineligible for study participation).
5) History of repeated muscle cramping (patients with such history will be identified and approached for study participation).
6) Past echocardiograms, if available, completed within 6 months prior to giving written informed consent. If there is echocardiographic data available, the following will be recorded for assessing and adjudicating atrial fibrillation events and any clinically significant cardiac arrhythmias, as available:
    a) Left ventricular ejection fraction (LVEF)
    b) Presence of distinct wall motion defects
    c) Estimated left end-diastolic pressure
    d) Distinct valvular abnormalities
    e) E/A (ratio of peak velocity blood flow from left ventricular relaxation in early diastole [E wave] to peak velocity flow in late diastole caused by atrial contraction [A wave]) and E/e' (ratio of transmitral early peak velocity [E] to early diastolic mitral annulus velocity [e'])
    f) Atrial cross-sectional diameter
    g) Right ventricular systolic pressure.
7) Negative pregnancy test for females of childbearing potential to confirm eligibility.

4.1.5 Physical Exam

A complete physical examination will be performed prior to the placement of the LINQ implantable recorder, with focus on general appearance, respiratory and cardiovascular systems, and lower extremities, and will include a limited neurological exam.

4.1.6 Vital Sign Measurements and Weight

Measurement of vitals is standard of care throughout each dialysis session, and will include blood pressure, pulse, weight, and body temperature.

Measurement of vitals and weight will be recorded post dialysis on Friday or Saturday prior to the long dialysis weekend and pre-dialysis on Monday or Tuesday after the long dialysis weekend.

4.1.7 12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG recording will be performed and used for confirmation of eligibility.

4.1.8 K^+ and PO_4 Piccolo POCT System Measurements (Weeks -4 and -3)

Patients will have blood draws completed prior to dialysis on two (2) separate occasions following the long dialytic "weekends" (i.e., on two consecutive Mondays for patients on a Monday-Wednesday-Friday dialysis schedule or on two consecutive Tuesdays for patients on a Tuesday-Thursday-Saturday dialysis schedule) during screening, before insertion of the cardiac loop recorder. Initial measurements of K^+ levels will occur real-time, using the Piccolo POCT system.

Patients with two (2) separate pre-dialysis Piccolo POCT measurements of K^+ between 5.1 and 6.5 mEq/L will be considered eligible for study participation and be allowed to proceed to placement of the implantable loop recorder. If one of the two screening pre-dialysis K+ levels is between 4.6 to 5.0 mEq/L or 6.6 to 7.0 mEq/L, the patient can undergo an additional whole blood Piccolo POCT K^+ measurement. Patients who fail the third whole blood Piccolo POCT K^+ measurement will be considered ineligible for study participation. Screen failures can be re-screened once to confirm eligibility in the study.

Note: K^+ and PO_4 Piccolo POCT may be performed several weeks after consenting depending on the need for a prohibited medication washout or whether the consenting process occurred on a day other than the Monday or Tuesday after the long dialysis weekend.

In addition, PO_4 will be measured by the Piccolo Xpress chemistry analyzer to determine incidence of hypophosphatemia (<3.0 mEq/L).

Piccolo POCT System

The Piccolo Xpress chemistry analyzer provides quantitative in-vitro determinations of clinical chemistry analytes in lithium-heparinized whole blood, heparinized plasma, or serum. The system consists of a portable analyzer and single-use disposable reagent discs. The analyzer (see figure below) contains the following features and components (see **Figure 7** below):

- A variable-speed motor to spin the reagent disc
- A photometer to measure analyte concentrations
- two microprocessors to control testing and analytical functions
- A thermal line printer to print out results
- A WVGA color touchscreen for communicating with the analyzer
- Optional data functions for more detailed analysis information

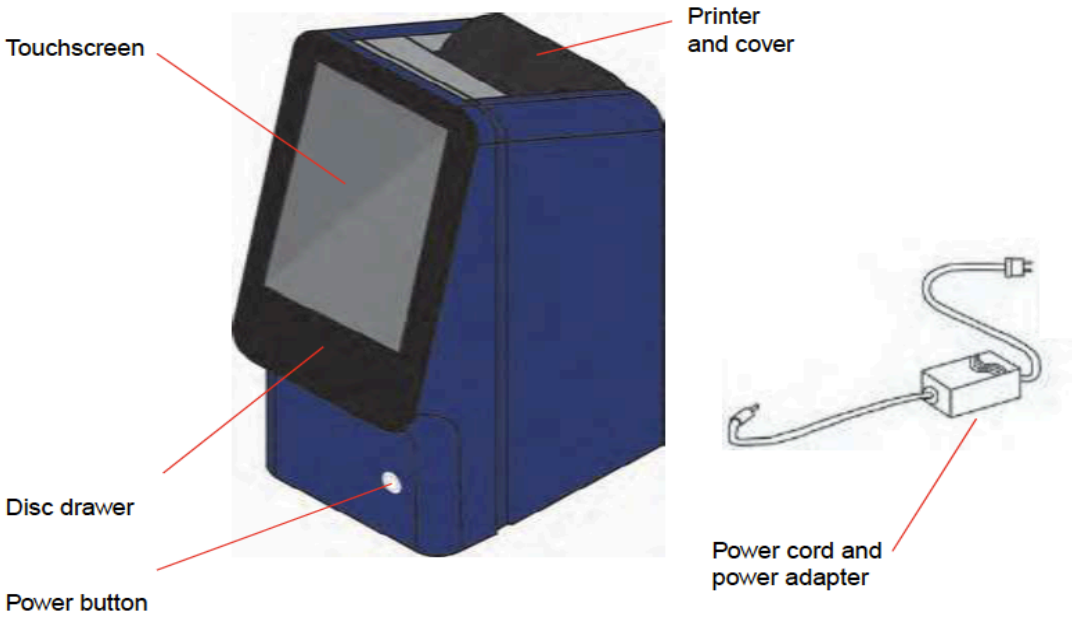


Figure 7 - Piccolo Xpress Chemistry Analyzer

Each reagent disc is self-contained clear plastic, 8 cm in diameter and 2 cm thick, and containing an aqueous diluent in its center and dry reagent beads in cuvettes around its edge. All blood separation and sample diluent mixing is performed within the disc itself.

To perform an analysis, the operator needs only to collect a blood sample (lithium-heparinized whole blood or plasma,), place the sample in the reagent disc, put the disc into the analyzer drawer on the front of the analyzer, and input patient information. When analysis is finished, the results print automatically.

Results are printed for inclusion within the patient's medical record. One Ethernet port and five USB ports are provided so data can be sent to an external printer, computer, memory stick, or laboratory information systems/electronic medical record systems (LIS/EMR).

The entire analysis requires ~100 µL of sample and is capable of providing results in about 12 minutes.

Please refer to the Piccolo Xpress Chemistry System Operator's Manual (provided separately from this protocol) for additional details on proper use and operation of the System. All System operators should familiarize themselves with the applicable sections in the operator's manual prior to conducting testing to assure safe and effective use of the Piccolo POCT System.

4.1.9 Insertion of the Cardiac Loop Recorder (Week -2)

Patients who have completed the screening assessments and are willing to proceed with study participation will be referred to a cardiac electrophysiologist (EP) or qualified implanter who is

trained and experienced in the placement of the LINQ device. It is anticipated that arranging for placement of the device (including scheduling and actual implantation) will take approximately 1-2 weeks, but may take up to 30 days. Please contact the sponsor if ILR placement will take longer then 30 days after the last qualifying Piccolo POCT K^+ System Measurements. The sponsor will determine on a case-by-case basis if an additional Piccolo POCT K^+ System Measurement is required prior to Baseline.

LINQ Device Insertion

As described in Section 8, patients with two (2) separate pre-dialysis Piccolo POCT measurements of K^+ between 5.1 and 6.5 mEq/L will proceed to scheduling and placement of a LINQ cardiac loop recorder. The research staff will schedule placement of the LINQ device with a participating EP cardiologist or qualified implanter on an "off-dialysis" day. As shown in **Figure 8**, the Medtronic Reveal LINQ™ implantable Loop recorder is a 1.7-inch-long rectangle shaped device that is placed subcutaneously (SQ) along the left parasternal border by a trained EP cardiologist or qualified implanter. This procedure requires only local anesthesia and is approximately 20 minutes in duration. Clinicians should follow the implant manuals when performing the Reveal LINQ implant.

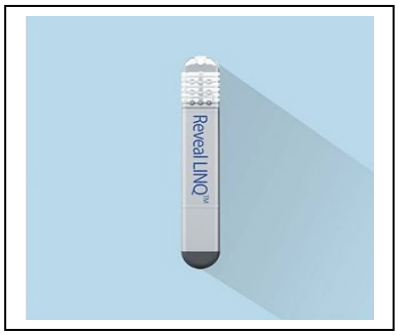


Figure 8 - LINQ Insertable Cardiac Monitor

After the LINQ device is implanted, it should be programmed to the study required settings specified below. The patient ID should be entered and it should be the CareLink Clinic code, followed by the device serial number.

It is recommended to choose "Cryptogenic Stroke" as the "Reason for Monitoring".

Programming Parameter	Required Setting
AT/AF Detection	On
Type	AF Only
AF Detection	Balanced Sensitivity
Ectopy Rejection	Aggressive
AT/AF Recording Threshold	All Episodes
Episode Priority	Tachy, Pause, Brady

Tachy Detection	On
Tachy Interval	130 bpm
Tachy Duration	16 beat
Brady Detection	On
Brady Interval	40 bpm
Brady Duration	4 beats
Pause Detection	On
Pause Duration	3 sec

*Recommended to be programmed to nominal settings that are automatically programmed with "Cryptogenic Stroke" as "Reason for Monitoring" with adjustments to Tachy and Brady Intervals.

Post-LINQ Device Insertion

For 2 weeks after LINQ device insertion, patients will be given time to heal and adapt to the device. During this 2-week blanking period, the device will measure continuous cardiac data, but it will not be interrogated and will not be used for analysis. During this blanking period, Medtronic will train study staff on how to interrogate and transmit LINQ device data, which will be sent to the Medtronic Monitoring Service; refer to the data flow shown in Figure 9.

After the 2-week ILR post-insertion recovery period, patients will be randomized to one of two treatment sequences, as described in Section 3.5. The day of randomization will be denoted as Study Day 1 and will also mark the start of Treatment Phase 1.

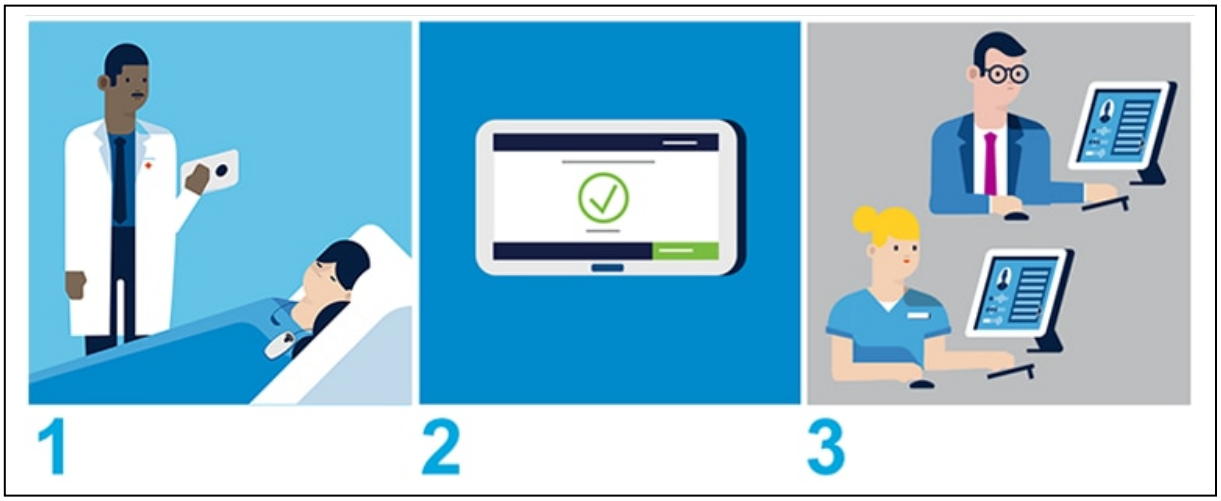


Figure 9 - Cardiac Monitoring Data Flow

1. Medtronic cardiac device is interrogated once a week in the dialysis clinic using the Patient Connector and the CareLink Express mobile app on a tablet.
2. The app will confirm that the transmission was successful.

3. Transmission will be read and triaged by the Medtronic Monitoring Service and sent to study Cardiologist for initial review.

4.2 Treatment period

Assessments during the treatment period will be carried out according to the schedule provided in **Table 1**.

After completing the 2-week post-ILR insertion blanking period, patients will be switched to the dialysate arm that they had been allocated to through randomization. After a 2-week "accommodation" period to the new dialysate (Weeks 1 and 2), the cardiac monitoring blanking period will be complete, and patient's ILRs will be interrogated weekly in order to download and transmit cardiac monitoring data. Patients will also undergo weekly Piccolo POCT blood draws initiated on Mondays or Tuesdays after their long dialysis weekends.

4.2.1 Blood Draws (Weeks 3 to 10 and Weeks 13 to 20)

During both 8-week treatment phases, the first twenty-five (25) patients randomized receiving standard treatment (hemodialysis using 2.0K^+/2.5 Ca^{++} dialysate bath, without Lokelma supplementation) will undergo blood collection for select chemistry tests and determination of protein-bound uremic toxins (PBUTs).

Blood will be drawn as follows:

1) A 4.0 ml Green Top tube will be drawn from the dialysis line after placement of the dialysis needles and BEFORE the initiation of dialysis. The Green Top tube will be in & out inverted 3 times and then used for Piccolo POCT measurements of K^+, $Ca^{++}$and PO_4, as described in Section 8. This will be repeated promptly before the anticipated termination of the dialysis session and within 30 minutes prior to rinse back.

2) Treatment Phase-1 only: Two 4.0 ml Purple Top tubes will be drawn from the first twenty-five (25) patients receiving standard treatment (hemodialysis using 2.0K^+/2.5 Ca^{++} dialysate bath, without Lokelma supplementation) by the same method (as described above) and centrifuged. Each tube of plasma (approximately 1ml after processing) will be transferred to a 1.0 ml O-Ring sealed cryovials (two cryovials pre-dialysis and two cryovials promptly before the anticipated termination of the dialysis session and within 30 minutes prior to rinse back) and frozen at -80^{o}C until analyzed for measurement of pre- and post-dialysis concentrations of the following PBUTs: p-Cresol sulfate (PCS), indoxyl sulfate, and asymmetric dimethylarginine (ADMA). Measurement of pre- and post-dialysis levels will be conducted by an outside vendor using gas chromatography-mass spectrometry (GC-MS) (*Tsikas et al. 2003*).

3) 5) A 5.0 ml Yellow Top SST tube will be drawn from the dialysis line promptly before the anticipated termination of the dialysis session (and within 30 minutes prior to rinse back) will be sent to the local laboratory for routine measurement of Mg^{++} levels.

4) A 2nd 4.0 ml Green Top tube will be drawn from the dialysis line promptly before the anticipated termination of the dialysis session (and within 30 minutes prior to rinse back) for Piccolo POCT measurement of post-dialysis electrolytes (K^+, Ca^{++} and PO_4), as described in Section 8.

5) A 5.0 ml Yellow Top SST tube will be drawn from the dialysis line promptly before the anticipated termination of the dialysis session (and within 30 minutes prior to rinse back) and will be sent to the local laboratory for routine measurement of Mg^{++} levels upon symptomatic muscle cramping (if possible).

4.2.2 Insertable Cardiac Loop Recordings (Weeks 3 to 10 and Weeks 13 to 20)

ILR interrogation will be initiated at the end of each 2-week accommodation period (to the new dialysate) and will continue throughout the two 8-week treatment phases. Devices will not be interrogated during either 2-week accommodation periods (following randomization and cross-over) and the data recorded during that time will not be used for analysis.

Patients will undergo LINQ device interrogation on a weekly basis, on each Monday or Tuesday after their long "dialysis weekend" throughout the two 8-week treatment phases. Each download session will occur prior to the pre-dialysis vital signs and weight measurements using the Patient Connector and the CareLink Express mobile app on a tablet. This process is anticipated to take less than 5 minutes. Data will not be reviewed at the time of interrogation.

Cardiac Data Monitoring

ILR will be interrogated weekly following the long "dialysis weekend" using the Patient Connector and the CareLink Express mobile app on a tablet. Cardiac data will be managed via the CareLink network and reviewed by the Medtronic Monitoring Service, where clinically relevant cardiac data will be identified and prioritized based on clinically actionable events. If a patient's arrhythmia meets any of the three CSCA categories, the principal study cardiologist and the site PI will be contacted to determine whether the patient requires further evaluation. Participating sites will receive copies of relevant cardiac events to enter into their patient's medical records.

Patients participating in the study may also receive a Patient Assistant, a hand-held, battery-operated telemetry device that enables the patient to activate the recording of cardiac information in the LINQ device while experiencing or immediately after a symptomatic event (see Figure 10). During the monitoring period, patients will be instructed to mark their symptom when they sense a tachyarrhythmia, bradycardia, or irregular heart rate. These events will be reviewed during the weekly LINQ device data download in order to determine if the symptoms were associated with a cardiac event.

Figure 10 – Patient Assistant

4.2.3 Cross-Over (Week 11)

At the end of the first treatment phase (Weeks 3 to 10) of the study, all blood draws will be stopped for 2 weeks. Cardiac loop recording devices will not be interrogated during this 2-week accommodation period, and the data recorded during that time will not be used for analysis. Patients who completed treatment with experimental 3.0 K^+/2.5 Ca^{++} dialysate with Lokelma supplementation (on off-dialysis days) during Treatment Phase-1 will be crossed over to standard 2.0 K^+/2.5 Ca^{++} dialysate with no Lokelma supplementation for Treatment Phase-2. Patients who completed treatment with standard 2.0 K^+/2.5 Ca^{++} dialysate with no Lokelma supplementation during Treatment Phase-1 will cross-over to experimental 3.0 K^+/2.5 Ca^{++} dialysate with Lokelma supplementation (on off-dialysis days) for Treatment Phase-2.

4.3 Follow-up period

Assessments during the Follow-up period will be carried out according to the schedule provided in Table 1.

After patients complete the 8-week Treatment Phase-2, all cardiac loop recording and non-standard of care blood draws will stop.

As part of the Follow-up, patients will be seen by the electrophysiologist (EP) cardiologist (or qualified implanter) for removal of the LINQ device unless they decide to leave it implanted. All equipment including the Care monitor recording device will be returned to the Sponsor.

For each patient, removal of the LINQ device marks the study completion (the end of their study participation).

5. STUDY ASSESSMENTS

The Investigators will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigators are responsible for the accuracy, completeness, and timeliness of the data recorded and of the answers to data queries according to the Research Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy Assessments

5.1.1 Atrial Fibrillation

As described in Section 2.1, the primary objective of this study is to determine whether increasing the K^+ concentration in a standard hemodialysis bath from 2.0 K^+/2.5 Ca^{++} to a 3.0 K^+/2.5 Ca^{++} composition with Lokelma will reduce the incidence of atrial fibrillation events.

Atrial fibrillation will be defined as irregular heart rhythms and irregular R-R intervals in the absence of definable P waves for a minimum of 6 minutes.

Atrial fibrillation events will be detected, recorded, and stored by the Medtronic LINQ device; see Section 4.1.8. This data will be downloaded on a weekly basis during both 8-week treatment periods (Treatment Phase-1 and Treatment Phase-2); see Section 4.2.2 for details.

Each atrial fibrillation event will be adjudicated and validated as a true atrial fibrillation event centrally by cardiologist who will be blinded to the treatment assignment.t.

5.1.2 Clinically Significant Cardiac Arrhythmias

As detailed in Section 2.2, the frequency and duration of post-dialysis CSCAs (defined as bradycardia, ventricular tachycardia and/or asystole) observed during experimental treatment compared to standard treatment will be evaluated as part of the secondary endpoints of the study.

CSCA events will be defined as follows:

- Bradycardia: Heart rate of ≤ 40 beats per minute (BPM) for a minimum duration of 6 seconds.
- Ventricular Tachycardia: Regular tachy-arrhythmia of ≥ 130 BPM for a minimum duration of 30 seconds
- Asystole: Absence of detectable ventricular conduction for a minimum of 3 seconds.

The occurrence of these typically silent arrhythmias will be detected, recorded, and stored by the Medtronic LINQ device; see description of the device in Section 4.1.8. Patients "sensing" a cardiac arrhythmia during dialysis will "mark" the event with the LINQ marking device. This data will be downloaded on a weekly basis during both 8-week treatment periods (Treatment Phase-1 and Treatment Phase-2); see Section 4.2.2 for details. Upon concluding that a cardiac arrhythmia is occurring, the dialysis technician will draw a Green Top and Tiger Red Top tubes from the dialysis line as the dialysis is being terminated.

All "patient marked" events will be adjudicated centrally by the reviewing cardiologist and reported to the Site PI if it considered that immediate attention is required.

5.1.3 Potassium Measurements

A further secondary objective of the study (see Section 2.2) is to determine whether the addition of oral sodium zirconium cyclosilicate (Lokelma®) during the 2-month treatment phase with the 3.0 K^+/2.5 Ca^{++} dialysate bath will reduce the number of days outside the "K^+ safety range" of 4.0 to 5.5 mEq/L compared to the 2-month treatment phase with the 2.0 K^+/2.5 Ca^{++} dialysate bath.

K^+ Piccolo POCT will be performed weekly during the two 8-week Treatment phases, as follows: pre-dialysis, and promptly before dialysis termination and 30 minutes prior to rinse back (along with Ca^{++} and PO_4 measurements); see Section 4.2.1.

5.1.4 Correlations Between Laboratory Parameters and Clinical Events

The study will also evaluate the correlation between PBUTs (PCS, indoxyl sulfate, and ADMA) and the frequency of atrial fibrillation events, as well as the correlation between electrolyte levels and clinical events (intradialytic hypotension, muscle cramping, and cardiac arrhythmias); see Section 2.4.

Measurements of PBUTs and electrolytes are described in Section 4.2.1. The recording and assessment of cardiac arrhythmias are detailed in Section 4.2.2 and Section 5.1.2, respectively.

The occurrence of other clinical events (intradialytic hypotension, muscle cramping) will be recorded during dialysis throughout the two 8-week treatment periods.

Intradialytic hypotension is defined as a systolic blood pressure (SBP) < 90 mmHg and any of the following events:

- A requirement to reduce the ultrafiltration rate
- A requirement for administration of a saline bolus
- Development of altered sensorium or level of alertness
- Onset of shortness of breath (SOB) or angina-like symptoms.

Muscle cramping is defined as any episode of painful muscle spasm that prompts the patient to alert the Dialysis staff of his/her discomfort.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood samples for determination of select clinical chemistry parameters will be collected and analyzed as indicated in the Study Plan (see Table 1).

As part of the safety objectives of the study, the number of hypokalemic events defined as Piccolo POCT or laboratory-measured K^+ of < 3.5 mEq/L, and the number of events of pre- or post-dialysis Ca^{++} < 2.5 Ca^{++} mEq/L , PO_4 levels <3.0 mEq/L and Mg^{++}< 2.0 mg/dL will be evaluated and compared between the two treatments (experimental vs standard); see Section 2.3.

All Piccolo POCT measurements will be completed locally. The Piccolo POCT device and methodology are described in Section 8, and the blood draws, including sample tubes and volumes collected are detailed in Section 4.2.1. In addition, the following laboratory variables will be measured at the site as part of the Piccolo POCT renal panel:

Table 2 Piccolo Renal Function Panel

Sodium (Na+)
Potassium (K+)
Phosphorus (PHOS)
Blood urea nitrogen (BUN)
Calcium (Ca^{++})
Albumin (ALB)
Glucose (GLU)

Creatinine (CRE)

Estimated Glumerular Filtration Rate (eGFR)

Chloride (Cl^-)

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.4.6.

5.2.2 Physical examination

As described in Section 4.1.5, at screening (prior to the placement of the implantable loop recorder), patients will undergo a complete physical examination that will focus on general appearance, respiratory and cardiovascular systems, and lower extremities, and will include a limited neurological exam. No subsequent physical exams will be mandated.

5.2.3 Cardiac Monitoring

In this study, continuous cardiac recordings will be performed as part of efficacy evaluations throughout the two 8-week treatment phases, using the Medtronic insertable loop recorder (ILR, LINQ device). Insertion of the cardiac loop recorder is described in Section 4.1.8. Cardiac data recordings are detailed in Section 4.2.2.

5.2.3.1 12-lead ECG

As indicated in Section 4.1.7, Standard resting 12-lead ECG recording will be performed at Screening only and used for confirmation of eligibility.

5.2.4 Vital signs

As indicated in Section 4.1.6, measurement of vitals is standard of care throughout each dialysis session, and will include blood pressure, pulse, and body temperature.

For information on how AEs based on vital signs measurements should be recorded and reported, see Section 6.4.6.

5.2.5 Other safety assessments – Concomitant Medications

All concomitant medications taken by the subject from the time of their consent signature will be recorded; see Section 7.7.

5.2.6 Pregnancy Test for Females of Childbearing Potential

As indicated in Section 4.1.4, a pregnancy test should be performed during screening for females of childbearing potential to confirm eligibility.

5.3 Safety Protocols

5.3.1 Safety Protocol for Patients with Piccolo POCT-Confirmed Hypokalemia or Hyperkalemia

Hyperkalaemia will be defined as a $K^+ \geq 7.0$ mEq/L and measured using Piccolo POCT technology in pre-dialysis obtained after the long dialysis "weekend". Unless clinically unstable, patients with hyperkalaemia will be dialyzed and managed according to the judgment of the Site PI. Dose adjustments of Lokelma will be with each patient prior to discharge.

Hypokalemia is defined as pre-dialysis K^+ level of < 3.5 mEq/L. Patients experiencing a minimum of two (2) hypokalemic events while taking Lokelma will have their Lokelma adjusted or discontinued at the discretion of the site PI.

Patients with clinically significant cardiac arrhythmias including bradycardia, ventricular tachycardia, and asystole that are recognized by the dialysis staff during an individual dialysis session will be managed according to site unit protocols and include necessary resuscitation and transfer to the nearest emergency department.

5.3.2 Safety Protocol for Patients with Intra-Dialytic Arrhythmias

Patients developing clinically apparent dialysis-associated arrhythmia including atrial fibrillation with or without with rapid ventricular response (RVR), atrial tachycardia (defined as sustained pulse >130 bpm), bradycardia (defined a symptomatic pulse of < 40 bpm) will be sent to the nearest emergency department for treatment at the discretion of the PI. All such events will be marked by the LINQ marking device.

If a complete metabolic panel is performed as standard of care, the results will be recorded in the patient's source chart and electronic data capture system (EDC).

5.3.3 Safety Protocol for Patients with Intra-Dialytic Hypotensive Events

All patients with a dialysis-associated hypotensive event (defined as a systolic blood pressure <90 mmHg) will be managed according to standard site unit protocols that may include:

a) The termination of all ultrafiltration

b) Administering a 500 ml saline bolus

c) Documenting the presence of altered sensorium or level of alertness

d) Documenting the presence of shortness of breath (SOB) or angina-like symptoms

All patients "sensing" a cardiac arrhythmia during dialysis will "mark" the event with the LINQ marking device.

If a complete metabolic panel is performed as standard of care, the results will be recorded in the patient's source chart and EDC.

Note: Should the patient quickly revive with the above listed maneuvers and the Site PI assesses that the patient can continue dialysis, the patient can complete their dialysis session.

5.3.4 Safety Protocol for Patients with Intra-Dialytic Symptomatic Muscle Cramping

A "symptomatic episode of muscle cramping" is defined as an event associated with any of the following:

a) Requirement to lower the dialysis ultrafiltration rate

b) Requirement for a saline bolus

c) Patient request to terminate dialysis (whether the dialysis session is stopped or not)

d) Decision to terminate dialysis.

Patient management during each of the above clinical scenarios will be left to the discretion of the site PI or according to existing protocols within the participating dialysis unit.

Upon onset of a "cramping event" the dialysis technician will follow typical dialysis unit protocols including reducing the ultrafiltration rate and giving a saline bolus. At this point the dialysis nurse or technician will draw a 5.0 ml Yellow Top SST tube from the dialysis line prior to the termination of the dialysis session, to be sent to the dialysis local lab for Mg^{++} and PO_4 levels (if possible).

All patients developing an episode of "symptomatic muscle cramping will "mark" the event with the LINQ marking device.

5.4 Pharmacokinetics

Not applicable. Pharmacokinetic samples will not be taken during the study.

5.5 Pharmacodynamics

Not applicable. Pharmacodynamic samples will not be taken during the study.

5.6 Pharmacogenetics

Not applicable. Pharmacogenetic samples will not be taken during the study.

5.7 Biomarker Analysis

Not applicable. There will be no collection and storage of donated biological samples for exploratory biomarker analysis.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

Please refer to section 4.2.2 and 5.1.2 for detail of how serious arrhythmias are detected and treated per the safety protocol and refer to section 5.3.2 for Patients with Intra-Dialytic Arrhythmias. ILR will be interrogated weekly following the long "dialysis weekend" using the Patient Connector and the CareLink Express mobile app on a tablet. Cardiac data will be

managed via the CareLink network and reviewed by the Medtronic Monitoring Service, where clinically relevant cardiac data will be identified and prioritized based on clinically actionable events. If a patient's arrhythmia meets any of the three CSCA categories, the principal study cardiologist and the site PI will be contacted to determine whether the patient requires further evaluation. Participating sites will receive copies of relevant cardiac events to enter into their patient's medical records.

6.1 Definition of Adverse Events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of Serious Adverse Event

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Note: Adverse events of malignant tumors reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement should be applied to clarify that the malignant tumour is a non-serious AE. For example, progression of a pre-existing tumour (i.e., included as medical history) during the study, that does not change treatment and/or prognosis of the malignant tumour, would be reported as an AE, but may not qualify for being assessed as serious. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed *via* cone biopsy.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the Investigator and reported to the Sponsor.

For further guidance on the definition of a SAE, see Appendix A (Additional Safety Information).

6.3 Definition of Suspected Unexpected Serious Adverse Event (SUSAR)

A suspected adverse reaction related to an Investigational Product (IP) that is both unexpected and serious.

6.4 Recording of adverse events

6.4.1 Time period for collection of adverse events

Adverse events will be collected from the time of first dose of Lokelma®, throughout the treatment and post-treatment follow-up period, up to the last study visit.

SAEs will be reported from the time the patient signed the Informed Consent Form.

6.4.2 Follow-up of unresolved adverse events

Any AEs that remain unresolved at the patient's last study visit will be followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. It is acknowledged that the Company may request additional information after the completion of the study.

6.4.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Intensity

  Adverse Event intensity will be assessed according to the following categories:

  - mild (awareness of sign or symptom, but easily tolerated)
  - moderate (discomfort sufficient to cause interference with normal activities)
  - severe (incapacitating, with inability to perform normal activities)
- Whether the AE is serious or not
- Investigator causality assessment /relationship to the study drug (yes or no)
- Action(s) taken with regard to the study drug
- AE caused the patient's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of SAE

- Reason for assessing the AE as serious
- For hospitalizations:
    - Date of hospitalization
    - Date of discharge
- For AEs with a fatal outcome:
    - Date of death
    - Probable cause of death
    - Autopsy performed and finding(s)
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of SAE.

Note: It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria outlined in Section 6.2. An AE of severe intensity would not necessarily qualify as serious. For example, nausea that persists for several hours may be considered severe, but not a SAE unless it meets the criteria provided in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE if it satisfies the criteria provided in Section 6.2.

6.4.4 Causality collection

The Investigator will assess causal relationship between the study drug and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A (Additional Safety Information).

6.4.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from study personnel: *'Have you had any health problems since your previous study visit?'* or revealed by observation will be collected and recorded in the eCRF. It is preferred that AE are recorded as diagnoses (when possible) rather than a list of signs and symptoms. However, if there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom should be recorded separately.

6.4.6 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs measurements will be summarized in the clinical study report. Deterioration from baseline in protocol-mandated

laboratory values or vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of study treatment.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator should use the clinical, rather than the laboratory term (e.g., anaemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or worsened (compared to baseline) clinically relevant abnormal physical examination findings should be reported as an AE.

6.5 Reporting of serious adverse events to the IRB and/or the Regulatory Authority

The Lokelma Package Insert serves as the Reference Safety Information (RSI) for this study.

All SAEs occurring from the time of consent and during the study have to be reported, whether or not considered causally related to the study drug.

The Investigator or designated site personnel must inform the designated Sponsor representative immediately (**no later than 24 hours**) after becoming aware of an SAE occurring in their study patient.

SAE reports should be submitted to the Sponsor representative using the following contact details:

The designated Sponsor representative will work with the Investigator to ensure that all necessary information is collected **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important/relevant information is missing, active follow-up must be undertaken immediately. The Investigator or designated site personnel must inform the Sponsor representatives of any follow-up information on a previously reported SAE immediately (**no later than 24 hours**) after receipt of the follow-up information.

Site PIs are responsible for informing the central Institutional Review Board (IRB) or their local IRB (as applicable) of SAEs as per their IRB requirements.

The Sponsor is responsible for informing the United States Food and Drug Administration (FDA), using the MedWatch/AdEERs form, of any serious or unexpected AEs that occur during the study, in accordance with the reporting obligations of 21 CFR 312.32. It is the responsibility of the Sponsor to compile all necessary information and ensure that submission of the safety report is completed within the FDA-mandated reporting timelines.

6.6 Reporting of Serious Adverse Events to Company

The Sponsor (NephroNet) is responsible for informing the Company (AstraZeneca) of all SAEs occurring during the study, whether or not considered causally related to the investigational product (IP). SAEs assessed as related to the IP must be provided to the Company on an ongoing

basis as individual case reports. SAEs unrelated to the IP must be provided to the Company in the form of quarterly listings.

SAE files (individual case reports and line listings) should be submitted along with a cover page to the following designated Company email address:

AEmailboxclinicaltrialTCS@astrazeneca.com

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to the Company at the same time these events are submitted to the FDA.

SAEs that do not require expedited reporting to the FDA/IRB still need to be reported to the Company as individual case reports on an ongoing basis (related SAEs) or provided in the form of quarterly listings (unrelated SAEs).

At the end of the study a final summary line listing of all SAEs submitted to the FDA and/or Company during the study, must be provided to the Company to enable reconciliation of safety information completed by the Company for its product.

6.7 Overdose

Overdose of the study drug (sodium zirconium cyclosilicate) (Lokelma®) could lead to hypokalemia. In case of suspected overdose (dosing above 15.0 g), potassium levels should be checked and potassium supplemented, as needed at the discretion of the PI.

The Investigator or designated site personnel must inform the Sponsor immediately (**no later than 24 hours**) of becoming aware of a study drug overdose.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4.

6.8 Pregnancy

All pregnancies and pregnancy outcomes should be reported to the Sponsor (NephroNet) and the Company (AstraZeneca) within the safety reporting guidelines.

6.8.1 Maternal exposure

If a patient becomes pregnant during the “high dialysate” treatment period, the study drug should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event. However, congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study.

The Investigator or designated site personnel must inform the Sponsor immediately (**no later than 24 hours**) of becoming aware of a pregnancy occurring in the study. All relevant pregnancy information should be provided to the Sponsor within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies. The same timelines apply when pregnancy outcome information becomes available.

6.8.2 Paternal exposure

Not applicable. There will be no requirements or restrictions associated with paternal exposure.

6.9 Management of IP-related Toxicities / Dose Reductions

The study drug (Lokelma) will be titrated from 5.0 grams per day (4 days/week) up to a maximum of 15.0 grams per day (4 days/week), to maintain K^+ within the desired target range (between 4.0 and 5.5 mEq/L). potassium levels will be regularly monitored, and the study drug dose adjusted based on the potassium levels (i.e., increased [up to a maximum of 15.0 grams/day] if potassium is >5.5 mEg/L, or decreased if potassium is <4.0 mEq/L).

As described in Section 3.9, the study drug will be permanently discontinued in case the patient develops any of the following IP-related events:

- Two (2) or more hypokalemic events (defined as pre-dialysis K+ level of < 3.5 mEq/L); <

Refer to Section 3.9 for further details on events requiring permanent discontinuation of the study drug.

Safety protocols for the management of intra-dialytic events are provided in Section 5.3.

6.10 Study Governance and Oversight

Responsibilities for the study design, protocol development, scientific oversight, and coordination of the study rest with the NephroNet as the responsible Academic Research Organization (ARO), and the National Coordinating PI (James A. Tumlin, MD).

No study committees will be established. Given the open label study design, and the underlying condition involving the management of routine and frequent complications of dialysis, site PIs will be responsible for all emergency medical decisions related to their study patients. Site PIs will meet with the National Coordinating PI on quarterly basis to review safety data and determine if changes to the protocol design or study conduct are required.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of Investigational Product(s)

The investigational product (IP) in this study is sodium zirconium cyclosilicate (Lokelma®), a potassium binder product for oral administration. It is indicated for the treatment of hyperkalemia in adults (*Lokelma United States Prescribing Information [USPI], 19th October 2021*).

Lokelma, powder for oral suspension will be supplied in 5.0 gram packets to study participants.

Investigational product	Dosage form and strength
sodium zirconium cyclosilicate (Lokelma®)	For oral suspension: 5 g of white to grey powder in a foil-lined packet.

Note: In this protocol, the terms investigational product, IP, and study drug are used interchangeably.

7.2 Dose and Treatment Regimens

7.2.1 Dosing Regimen

Patients will take Lokelma supplementation on off-dialysis days (4 days/week) while receiving hemodialysis with 3.0 K^+/2.5 Ca^{++} mEq dialysate bath (8-week treatment phase):

- Patients on a Monday-Wednesday-Friday dialysis schedule will take the study drug on Tuesday, Thursday, Saturday, and Sunday
- Patients on a Tuesday-Thursday-Saturday dialysis schedule will take the study drug on Monday, Wednesday, Friday, and Sunday.

The individual starting dose will be 5.0 grams (4 days/week), and will be titrated weekly in 5.0 gram increments up to a maximum of 15.0 grams (4 days/week) to maintain K^+ within the desired target range (between 4.0 and 5.5 mEq/L):

- Patients who fail to achieve a pre-dialysis K^+ of $\leq$ 5.5 mEq/L after one week of 5.0 grams Lokelma will be treated with 10.0 grams on off-dialysis days for an additional 7 days.
- Patients failing to achieve a pre-dialysis K+ of $\leq$ 5.5 mEq/L after one week of 10.0 grams Lokelma will have their study drug dose increased to 15.0 grams.
- Patients failing to achieve the target K^+ after a 7-day course of 15.0 grams Lokelma on off-dialysis days will be considered a treatment failure and withdrawn from the study.

Potassium levels will be regularly monitored throughout the 8-week treatment phase, and the study drug dose adjusted based on the potassium levels (i.e., increased [up to a maximum of 15.0 grams/day] if potassium is >5.5 mEq/L, or decreased if potassium is <4.0 mEq/L).

7.2.2 Study Drug Dispensation and Instructions for Reconstitution and Dosing

The allow for adequate dosing (including dose-titration, as described in Section 7.2.1), the study drug will be dispensed to patients on a weekly basis, as follows:

Table 3 IP Dispensing Schedule and Dosing Instructions

IP Dose Level	IP Packets dispensed	Instructions for Patients (For dosing on off-dialysis days):
5.0 grams, 4 days/week	4 x 5.0 g packets	On each dosing day (4 off-dialysis days per week): Dissolve in water and drink the content of one 5.0 gram packet [1]
10.0 grams, 4 days/week	8 x 5.0 g packets	On each dosing day (4 off-dialysis days per week): Dissolve in water and drink the content of two 5.0 gram packet [1]
15.0 grams, 4 days/week	12 x 5.0 g packets	On each dosing day (4 off-dialysis days per week): Dissolve in water and drink the content of three 5.0 gram packet [1]

[1] Patients should be instructed to (i) empty the entire contents of the packet(s) into a drinking glass containing approximately 3 tablespoons of water or more if desired; (ii) stir well and drink immediately; (iii) if powder remains in the drinking glass, add water, stir, and drink immediately; (iv) repeat until no powder remains to ensure the entire dose is taken.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions, at a temperature between 15°C-30°C (59°F-86°F). The study drug label will specify the appropriate storage conditions.

At the study site, study drug will be stored at the participating dialysis unit, separate from other similar agents (Patiromer).

7.5 Compliance

During the 8-week "high dialysate" treatment period, patients will be asked to return to the site all used (including empty) packets of study drug (Lokelma) on a weekly basis. These will be assessed by the study coordinator to confirm treatment compliance. In case of a discrepancy between the planned vs actual number of packets used, the patient will be asked whether they had missed any of the prescribed study drug doses. Information about missed doses will be recorded in the patient's source records. An additional "internal control" of study drug compliance will be the pre-dialysis K^+ level after the long dialysis weekend. Patients reporting compliance with the study drug but K^+ above the 5.5 mEq/L goal will be up-titrated to the next Lokelma dose.

Study drug administration should also be recorded in the appropriate section of the eCRF.

7.6 Accountability

The study drug (Lokelma) provided for this study will be used only as directed in this protocol.

The study nurse coordinator will be responsible for recording all study drugs dispensed to and returned by the patient. Any unused packets of study drug will either be returned to the Company under the directive of the Company, or destroyed locally upon approval by the Company, and according to applicable local Standard Operating Procedures (SOPs).

7.7 Concomitant and Other Treatments

All concomitant medications must be recorded in the appropriate sections of the eCRF.

7.7.1 Prohibited Treatment

Use of the following medications is prohibited during the study:

Prohibited Medication/Class of drug	**Washout Period***
Amiodarone or other anti-arrhythmic therapy	2 weeks prior to Screening

Patiromer or other drugs for treatment of hyperkalemia	1 week prior to Screening

*Washout of the of the prohibited medications can occur after signing of informed consent as applicable.

7.7.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator, and recorded in the appropriate sections of the Case Report Form.

The study drug (Lokelma) can transiently increase gastric pH, and as a result, it can change the absorption of co-administered drugs that exhibit pH-dependent solubility. Therefore, patients who are taking other oral medications will be advised to take these medications at least 2 hours before or 2 hours after the study drug.

7.8 Post Study Access to Study Treatment

Not applicable.

8. STATISTICAL ANALYSES

8.1 Statistical Considerations

Analyses will be performed by the Sponsor or its representatives.

A comprehensive Statistical Analysis Plan (SAP) may be prepared within 90 days of the date of the first participant enrolled, and any further changes during the course of the study will be included (reflecting the final Clinical Study Protocol, including any amendments) prior to clinical database lock.

The SAP will include a more technical and detailed description of the statistical analyses described in the following sections.

8.2 Sample Size Estimate

The primary statistical hypothesis of the study is that the rate of atrial fibrillation events during hemodialysis using the 3.0 K^+ dialysate bath supplemented with sodium zirconium cyclosilicate (Lokelma®) is not equal to the rate of events incurred during hemodialysis using the 2.0 K^+ dialysate bath.

The sample size estimation is based upon the primary statistical hypothesis, and its details were separately documented.

With >90% power to reject the primary hypothesis, 40 subjects would need to be randomized into one of two treatment sequences in the 2x2 cross-over study using the simulation study with a 2-sided alpha of 0.05, assuming an event rate of 4.6 with the 2.0 K^+ dialysate bath, an overdispersion parameter of 0.07 and a reduction of rate ratio of 25%. It is expected that 10% of randomized subjects will not complete both study periods. Accounting for this estimated 10%

attrition rate, **44 subjects** per treatment sequence or **88 subjects** in total will be randomized in the study.

8.3 Definitions of Analysis Sets and Analysis Periods

The analysis of data will be based on different analysis sets according to the purpose of analysis, i.e., efficacy or safety.

8.3.1 All-participants Analysis Set

The all-participants analysis set will consist of all participants who were screened for the study.

8.3.2 Full Analysis Set

The Full Analysis Set (FAS) will include all randomized participants, with participants being analyzed as randomized, rather than as treated. All efficacy endpoints will be analyzed using the FAS.

8.3.3 Safety Analysis Set

The Safety Analysis Set will include all randomized participants who during the first treatment period (study Phase I): (i) received at least one dose of the study drug (Lokelma) during treatment with the 3.0 K^+ dialysate bath; or (ii) completed Visit 2 during treatment with the 2.0 K^+ dialysate bath. All safety endpoints will be analyzed using the SAS.

The number of participants in each analysis set, and the number excluded and associated reasons will be summarized by treatment group and overall. In addition, the following periods will be defined for the purpose of reporting:

Table 4 Analysis Periods

	Treatment Phase-1	**Treatment Phase-2**
Treatment Sequence A	3.0K^+ dialysate bath + SZC	2.0K^+ dialysate bath
Treatment Sequence B	2.0K^+ dialysate bath	3.0K^+ dialysate bath + SZC

Abbreviations: SZC = sodium zirconium cyclosilicate (Lokelma®)

8.4 Outcome Measures for Analyses

8.4.1 Primary Efficacy Endpoint: Frequency of Atrial Fibrillation Events

The primary efficacy endpoint is the frequency of atrial fibrillation events occurring during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 dialysate cross-over periods. Atrial fibrillation will be defined as irregular heart rhythms and irregular R-R intervals in the absence of definable P waves for a minimum of 6 minutes. Each atrial fibrillation event will be adjudicated and validated as a true atrial fibrillation event by a central cardiologist who is blinded to dialysate K^+ content.

The total number of atrial fibrillation events will be compared between the two dialysate groups.

The primary objective of the study will have been achieved if the frequency of atrial fibrillation events occurring during experimental treatment (hemodialysis using 3.0K^+/2.5 Ca^{++} dialysate bath, with Lokelma supplementation on off-treatment days) is lower compared to standard treatment (hemodialysis using 2.0K^+/2.5 Ca^{++} dialysate bath, without Lokelma supplementation).

8.4.2 Secondary Efficacy Endpoint #1: Frequency and duration of Clinically Significant Cardiac Arrhythmia Events

Frequency and duration of CSCAs (bradycardia, ventricular tachycardia and/or asystole) events during the 8-week Phase-I dialysate cross-over period and the 8-week Phase-II cross-over period is a secondary efficacy endpoint. Definitions of CSCA events are provided in Section 5.1.2.

This secondary objective will have been achieved if the frequency of post-dialysis CSCAs event (bradycardia, ventricular tachycardia and/or asystole) is lower during experimental compared to standard treatment or if a total duration of post-dialysis CSCAs event (bradycardia, ventricular tachycardia and/or asystole) is shorter during experimental compared to standard treatment.

8.4.3 Secondary Efficacy Endpoint #2: Events Outside the Optimal K^+ "Window"

The number of events of K^+ outside of the 4.0 to 5.5 mEq/L safety range is a secondary efficacy endpoint in this study, The total number of events of pre- or post-dialysis K^+ falling outside the "K^+ safety range" will be averaged and compared between the two dialysate groups.

The study aims to show that patients experience less risk of K^+ falling outside the range of 4.0 to 5.5 mEq/L while receiving experimental compared to standard treatment.

8.4.4 Exploratory Efficacy Endpoint #1:Relationship Between PBUTs and Atrial Fibrillation Rates

The study will also evaluate the correlation between PBUTs (indoxyl sulfate, PCS, and ADMA) and the frequency of atrial fibrillation events.

8.4.5 Exploratory Efficacy Endpoint #2: Correlation Between Electrolytes and Clinical Events

The following correlations will be explored:

- Correlation between electrolyte levels and clinical events (intradialytic hypotension, muscle cramping, and cardiac arrhythmias).
- Correlation between electrolytes falling below threshold levels (Ca^{++} < 7.0 mEq/L, PO_4 levels <3.0 mEq/L, Mg^{++}< 2.0 mg/dl, and K^+ of < 3.5 mEq/L) and clinical events (cardiac arrhythmias).

8.4.6 Safety Endpoint #1: Lokelma Induced Hypokalemia

To evaluate whether the use of Lokelma during periods when patients are receiving a 3.0 K^+/2.5 Ca^{++} bath is associated with hypokalemic events, the total number of hypokalemic events (defined as Piccolo POCT or laboratory-measured K^+ of < 3.5 mEq/L) will be summarized.

8.4.7 Safety Endpoint #2: Incidence of Dialysis-related Hypokalemia, Hypomagnesemia, Hypophosphatemia, or Low Calcium

This endpoint is defined as the number of events promptly prior to the termination of dialysis where a Piccolo POCT measurement of K^+ is < 2.0 mEq/L OR Ca^{++} is < 7.0 mEq/L, OR Mg^{++} is < 2.0 mg/dl OR a PO_4 level is <3.0 mEq/L.

All episodes where a specific electrolyte falls below the above listed threshold will be considered an "event" for that electrolyte. The total number of "events" will be recorded during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 cross-over periods. Each electrolyte will be its own "safety" objective independently.

8.4.8 Safety Endpoint #3: Adverse Experiences

The frequencies of AEs, SAEs, and withdrawals due to AEs will be summarized, with focus on treatment-related events.

8.5 Methods for statistical analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

8.5.1 General Considerations

Inference concerning the primary analysis will be performed at the 2-sided 5% significance level. All point estimates will be presented together with confidence intervals of 2-sided 95% coverage.

The analysis assumes that there is no carry-over effect given that the wash-out period is deemed appropriate to rule out this effect by design.

Intercurrent events are handled as outlined within each section for the primary and secondary endpoint analyses below. For the primary endpoint and secondary endpoints, missing data will occur in the case where participants are lost to follow-up, provide insufficient evaluable data, withdraw consent, or die during the study. The proportion of participant missing data will be presented as appropriate.

For each participant, baseline is defined as the last available assessment prior to or on the date of the randomization visit, unless otherwise specified. A period baseline is defined as the last available assessment prior to or on the date of each of periods

In general terms, the Full Analysis Set (FAS) will be used for the efficacy analyses and the Safety Analysis Set will be used for the safety analyses.

In general, all baseline characteristics and efficacy and safety variables will be summarized using descriptive statistics as appropriate. Continuous variables will be summarized by descriptive statistics including number of participants (n), mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequencies and percentages, where the denominator of the calculation is the underlying analysis set population unless otherwise stated.

Descriptive statistics of quantitative efficacy and safety parameters by scheduled visits will be provided on observed cases (i.e., including only participants who have non-missing assessments at a given visit).

8.5.1.1 COVID Considerations

It is anticipated that additional sensitivity and supplementary analyses will be required to determine the impact of the COVID-19 pandemic on this trial and its endpoints. Planned sensitivity analyses will distinguish between pandemic and non-pandemic-related intercurrent events in terms of the approach taken for sensitivity analyses. Further details will be included in the SAP.

8.5.2 Analysis of the Primary Variable

The primary efficacy endpoint is the frequency of atrial fibrillation events occurring during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 dialysate cross-over periods.

The primary analysis will test the null hypothesis that there is no difference in the rate of atrial fibrillation events between the $3.0K^+$ dialysate bath with Lokelma and the $2.0K^+$ dialysate bath without Lokelma, against the alternative hypothesis that there is a difference in the rate of atrial fibrillation events between the $3.0K^+$ dialysate bath with Lokelma and the $2.0K^+$ dialysate bath without Lokelma. Statistical hypothesis testing will be completed at a 2-sided 0.05 significance level.

The primary analysis will not account for missing values. However, sensitivity analyses will be conducted using the pattern mixture model with multiple imputation (PM-MI) method. Details of the PM-MI method will be provided in the SAP.

A generalized linear model assuming the distribution of negative binomial will be used, with fixed effect terms for the treatment groups ($3.0K^+$ dialysate bath with Lokelma and $2.0K^+$ dialysate bath without Lokelma), the study period, and log (the duration of period) as an offset variable1. An unstructured working variance-covariance will be employed. Additional model terms may be included, details of which will be described in the SAP. The estimated risk ratio between groups and its 95% robust confidence interval (CI) will be displayed. The null hypothesis will be rejected if the p-value (based upon the Wald statistics) is less than 0.05.

8.5.3 Analysis of the Secondary Variables

Each secondary endpoint will be analyzed individually, and no multiplicity control will be applied. Analyses of secondary variables will not account for missing values.

The secondary endpoint of clinically significant arrhythmia events will be analyzed similarly to the primary endpoint.

The secondary endpoint of a total duration of clinically significant arrhythmia events will be analyzed by a linear mixed model. Details of the model specifications will be in the SAP

The secondary endpoint of risk of outside K^+ safe range will be analyzed with a similar approach of the primary endpoint but with a logit link function. Details of the model specification will be included in the SAP.

A nominal p-value and a 95% C.I. of the effect between two treatment groups will be reported for each of secondary endpoints.

8.5.4 Analysis of the Exploratory Variables

All exploratory endpoints will be analysed using the FAS. A full description of the exploratory endpoints and analyses will be included in the SAP.

8.5.5 Subgroup analysis

The primary and select secondary variables may be analyzed based on the following pre-defined subgroups:

1) ESRD patients with diabetes mellitus:

Patients with diabetic nephropathy as their proximate cause of ESRD will be pre- identified as a group of patients with increased risk for post-dialysis atrial fibrillation.

2) ESRD patients with a prior history of atrial fibrillation:

Patients with a history of atrial fibrillation but in stable sinus rhythm will be pre- identified as a group with increased risk for post-dialysis atrial fibrillation.

3) ESRD Patients with grade II or higher levels of diastolic dysfunction

Patients with echocardiogram-defined grade II diastolic dysfunction are defined as having an E/e' ratio of > 12 within 12 months of study entry.

4) ESRD patients with confirmed left ventricular hypertrophy (LVH)

Patients with LVH are defined as having left ventricular wall thickness > 1.2 cm confirmed by echocardiogram within 12 months of study entry.

8.5.6 Safety Analyses

Lokelma-induced hypokalemia will be evaluated based on the total number of hypokalemic events defined as Piccolo POCT or laboratory-measured K^+ of < 3.5 mEq/L.

The incidence of dialysis-related hypokalemia, hypomagnesemia, hypophosphatemia, and low calcium will be evaluated based on the number of events promptly prior to the termination of dialysis where a Piccolo POCT measurement of K^+ is < 2.0 mEq/L OR Ca^{++} is < 7.0 mEq/L, OR Mg^{++} is < 2.0 mg/dl, OR a PO_4 level is <3.0 mEq/L. All episodes where a specific electrolyte falls below the above listed threshold will be considered an "event" for that electrolyte. The total number of "events" will be recorded during the 8-week Treatment Phase-1 and the 8-week Treatment Phase-2 cross-over periods and compared between the treatments.

Safety will also be assessed in terms of the frequency of AEs, SAEs, and withdrawals due to AEs, with focus on treatment-related events. Appropriate summaries of these data will be presented by treatment group and/or study period.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). A treatment-emergent AE

(TEAE) is defined as an AE with the start date on or after the first dose date and up to (and including) 14 days after the last dose date in each of study periods when patients received 3K Bath with Lokelma. However, when patients received 2K Bath without Lokelma, A treatment-emergent AE (TEAE) is defined as an AE with the start date on or after the first visit date and up to (and including) 14 days after the last visit date in each of study periods. Only TEAEs will be included in table summaries.

The number and percentage of participants experiencing AEs, SAEs, AEs that led to withdrawal, AEs that led to death, and the number of such events, will be summarised by SOC, PT, and treatment group and study period. The number and percentage of participants experiencing AEs will further be summarised by intensity and will be presented with the number of events at each level of intensity.

Additionally, the number and percentage of participants with AEs leading to discontinuation of Lokelma will be presented by SOC and PT, and the number and percentage of participants with any AE will be presented by SOC, PT, and relationship to Lokelma as assessed by the investigator. Each of these summaries will also include the number of events.

All AEs, SAEs, AEs that led to withdrawal or death and treatment-related AEs will be included in per-patient listings.

Clinical safety laboratory assessments will be summarised and listed. Shift tables will be provided for select tests, where shift from screening baseline to the worst value within each of study periods will be summarised. Laboratory data outside the reference ranges will be indicated in all listings.

All safety analyses will be performed on the Safety Set. In general, safety assessments will be reported descriptively by treatment group and/or study period. Full details on safety analyses will be provided in the SAP.

8.5.7 Interim analysis

No interim analysis is planned.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first patient is entered into the study, a Sponsor representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and train them in any study-specific procedures.

The site PI will ensure that appropriate training relevant to the study is given to all study staff at their site, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The site PI will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.2 Monitoring of the study

Site management and monitoring will be the responsibility of the Sponsor (NephroNet). During the study, a Sponsor representative will have regular contacts with the study sites, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study), including verification of informed consent of participants. This will require direct access to all original records for each study patient (e.g., clinic charts)

The Sponsor representative will be available between visits if the Investigator(s) or other staff at the study site needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Research Agreement for location of source data.

9.2.2 Research Agreement(s)

Site PIs should comply with all the terms, conditions, and obligations of the Research Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Research Agreement, the terms of the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients. In all other respects, not relating to study conduct or treatment of patients, the terms of the Research Agreement shall prevail.

Agreements between the Sponsor and the site PI should be in place before any study-related procedures can take place, or patient are enrolled.

9.2.3 Archiving of study documents

The Sponsor follows the principles outlined in the Research Agreement (RA).

The study site/site PI will retain the essential documents specified in the Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH) (e.g., source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site as per regulatory obligations for a Phase IV clinical trial, and thereafter destroyed after approval from the Sponsor.

9.2.4 Deviation from the clinical study protocol

The Investigator(s) must not deviate from or make any changes to the protocol without documented approval from the Sponsor and the reviewing IRB, except in case of a medical

emergency, where the deviation or change is necessary to avoid an immediate hazard to study patients. In such case, the site PI must provide details of the deviation or change (including reason), and the proposed revision(s) to the protocol, to the Sponsor and IRB as soon as possible, in order to obtain their approval.

All deviations from the protocol should be documented in the eCRF regardless of their reasons.

9.3 Study Timetable and End of Study

The end of the study is defined as Last Patient Last Visit (LPLV).

The study is expected to start in April 2022 and to end by end of June 2023.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. The Sponsor may also terminate the entire study prematurely if concerns for patient safety arise within this study.

9.4 Data Management

Data management activities will be performed by according to the Data Management Plan.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the current version of the World Health Organization (WHO) Drug Dictionary. Classification coding will be performed by a designated Consultant Medical Coder.

The data collected through third party sources will be obtained and reconciled against study data. Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, and locked, clean file will be declared, and the clinical database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports will be produced and reconciled with the study clinical database.

Management of external data

During both 8-week treatment phases, ILR will be interrogated weekly following the long "dialysis weekend" using the Patient Connector and the CareLink Express mobile app on a tablet, as described in Section 4.2.2. Cardiac data will be managed via the CareLink network and reviewed by the Medtronic Monitoring Service, where clinically relevant cardiac data will be identified and prioritized based on clinically actionable events. Refer to Section 4.2.2 for details.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

10.2 Patient Data Protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Patients will be informed that all study data will be stored in secure password-protected computer databases, and patient confidentiality will be maintained as mandated by Federal Law.

10.3 Ethics and Regulatory Review

10.3.1 Ethics Review

Appropriate written IRB approval must be obtained for the final study protocol and Informed Consent Form, as well as any other written information and/or materials to be provided to study patients (e.g., advertising used to recruit patients for the study). The site PI will be responsible for submitting these documents to the applicable IRB, and for providing the written IRB approval to the Sponsor before enrollment of any patient into the study.

The Sponsor (NephroNet) should approve any modifications to the Informed Consent Form template that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB annually.

The Sponsor will provide IRBs and site PIs with safety updates/reports according to local requirements. Each site PI is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. The Company (AstraZeneca) will provide this information to the site PIs so that they can meet these reporting requirements.

10.3.2 Regulatory Review

The National Coordinating PI (James A. Tumlin, MD) submitted the Investigational New Drug (IND) application to the FDA, and the FDA ruled that this study is IND exempt.

10.4 Informed consent

Investigators will ensure that:

- Each patient is given full and adequate oral and written information about the nature, purpose, possible risks, and benefits of the study
- Each patient is explained that they are free to discontinue from the study at any time
- Each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- A copy of the signed Informed Consent Form is given to the patient
- Any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by the IRB.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without approval from the Sponsor.

If there are any substantial changes to the study protocol, these changes will be documented in a study protocol amendment. The amendment is to be approved by the relevant IRB. The Sponsor will distribute the protocol amendment to each site PI for submission to their IRB; see Section 10.3.

If a protocol amendment requires a change to a site's Informed Consent Form, the Sponsor and the site's IRB are to approve the revised Informed Consent Form before it is used.

Administrative change(s) will be communicated to each IRB as per local requirements.

10.6 Audits and inspections

Authorized representatives of the Sponsor, a regulatory agency, or an IRB may perform site audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any applicable regulatory requirements. The Investigator will notify the Sponsor immediately if contacted by a regulatory agency about an inspection at the center.

11. LIST OF REFERENCES

Airy M, Schold JD, Jolly SE, *et al*. Cause-Specific Mortality in Patients with Chronic Kidney Disease and Atrial Fibrillation. *Am J Nephrol*. 2018;48(1):36-45. doi:10.1159/000491023

Aoki K, Teshima Y, Kondo H, *et al*. Role of Indoxyl Sulfate as a Predisposing Factor for Atrial Fibrillation in Renal Dysfunction. *J Am Heart Assoc*. 2015 Oct 9;4(10):e002023. doi: 10.1161/JAHA.115.002023.

Avari Silva JN, Bromberg BI, Emge FK, *et al*. Implantable Loop Recorder Monitoring for Refining Management of Children With Inherited Arrhythmia Syndromes. *J Am Heart Assoc*. 2016 May 26;5(6):e003632. doi: 10.1161/JAHA.116.003632.

Diggle PJ, Heagerty P, Liang K-Y, and Zeger S. (2001) Analysis of Longitudinal Data. 2nd edition, Oxford University Press

Fishbane S, Ford M, Fukagawa M, *et al*. A Phase 3b, Randomized, Double-Blind, Placebo-Controlled Study of Sodium Zirconium Cyclosilicate for Reducing the Incidence of Predialysis Hyperkalemia. J Am Soc Nephrol. 2019 Sep;30(9):1723-1733. doi: 10.1681/ASN.2019050450.

Krijthe BP, Heeringa J, Kors JA, *et al*. Serum potassium levels and the risk of atrial fibrillation: the Rotterdam Study. *Int J Cardiol*. 2013 Oct 15;168(6):5411-5. doi: 10.1016/j.ijcard.2013.08.048.

Ohnishi T, Kimachi M, Fukuma S, *et al*. Postdialysis Hypokalemia and All-Cause Mortality in Patients Undergoing Maintenance Hemodialysis. *Clin J Am Soc Nephrol*. 2019 Jun 7;14(6):873-881. doi: 10.2215/CJN.07950718.

Pun PH, Lehrich RW, Honeycutt EF, *et al*. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. *Kidney Int.* 2011 Jan;79(2):218-27. doi: 10.1038/ki.2010.315.

Roy-Chaudhury P, Tumlin JA, Koplan BA, *et al*; MiD investigators and committees. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. *Kidney Int.* 2018 Apr;93(4):941-951. doi: 10.1016/j.kint.2017.11.019.

Sacher F, Jesel L, Borni-Duval C, *et al*. Cardiac Rhythm Disturbances in Hemodialysis Patients: Early Detection Using an Implantable Loop Recorder and Correlation With Biological and Dialysis Parameters. *JACC Clin Electrophysiol*. 2018 Mar;4(3):397-408. doi: 10.1016/j.jacep.2017.08.002.

Severi S, Pogliani D, Fantini G, *et al*. Alterations of atrial electrophysiology induced by electrolyte variations: combined computational and P-wave analysis. *Europace*. 2010 Jun;12(6):842-9. doi: 10.1093/europace/euq042.

Soliman EZ, Prineas RJ, Go AS, *et al*. Chronic kidney disease and prevalent atrial fibrillation: the chronic renal insufficiency cohort (CRIC). *Am Heart J* 2010;159:1102–1107. doi: 10.1016/j.ahj.2010.03.027.

Tsikas D, Schubert B, Gutzki FM, *et al*. Quantitative determination of circulating and urinary asymmetric dimethylarginine (ADMA) in humans by gas chromatography-tandem mass spectrometry as methyl ester tri(N-pentafluoropropionyl) derivative. J Chromatogr B Analyt Technol Biomed Life Sci. 2003 Dec 5;798(1):87-99. doi: 10.1016/j.jchromb.2003.09.001.

Tang WH, Wang CP, Chung FM, *et al*. Uremic retention solute indoxyl sulfate level is associated with prolonged QTc interval in early CKD patients. *PLoS One*. 2015;10(3):e0119545. Published 2015 Apr 20. doi:10.1371/journal.pone.0119545

Writing Group Members; Mozaffarian D, Benjamin EJ, Go AS *et al*; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics-2016 update: A report from the American Heart Association. *Circulation*. 2016 Jan 26;133(4):e38-360. doi: 10.1161/CIR.0000000000000350.

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious. Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When assessing causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug:

- Exposure to suspect drug: Has the patient actually received the suspect drug?
- Time Course: Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile: Was the AE consistent with previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Could the AE be anticipated from its pharmacological properties?
- De-challenge experience: Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause: The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience: Did the AE reoccur if/when the suspected drug was reintroduced after it had been stopped? Sponsor would not normally recommend or support a re-challenge.
- Laboratory tests: A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Not applicable.

Appendix C Pharmacogenetics Research

Not applicable.