Clinical Trial Protocol: 1407-004

Study Title:	Clinical Evaluation of Use of Prismocitrate 18 in Patients Undergoing Acute Continuous Renal Replacement Therapy (CRRT)
Study Number:	1407-004
Study Phase:	III
Product Name:	Prismocitrate 18
IND Number:	126083
Indication:	Prismocitrate 18 is intended to be used as a replacement solution for regional anticoagulation of the extracorporeal circuit in patients undergoing continuous renal replacement therapy (CRRT).
Investigators:	Multicenter-up to 15 sites in the United States and Canada.
Sponsor:	Baxter Healthcare Corporation
Sponsor Contact:	[redacted], MS [redacted] Baxter Healthcare Corporation Mobile: [redacted] Email: [redacted]
Medical Monitor:	[redacted], MD Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015 Tel: [redacted] Mobile: [redacted] Email: [redacted]

	Date
Original Protocol:	2016 FEB 08
Amendment 1:	2016 MAY 20
Amendment 2:	2017 JAN 05
Amendment 3:	2018 FEB 08

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[redacted]

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SYNOPSIS

Sponsor:
Baxter Healthcare Corporation

Name of Finished Product:
Prismocitrate 18

Name of Active Ingredient:
Prismocitrate containing 18 mmol/L trisodium citrate

Study Title:
Clinical Evaluation of Use of Prismocitrate 18 in Patients Undergoing Acute Continuous Renal Replacement Therapy (CRRT)

Study Number:
1407-004

Study Phase: III

Primary Objective(s):
The primary objective of this study is to evaluate the efficacy of Prismocitrate 18 in prolonging extracorporeal circuit life in patients treated with continuous renal replacement therapy (CRRT). The Control Group will be patients receiving CRRT with no anticoagulation.

Secondary Objectives:
The secondary objectives of this study are to:

- evaluate the efficacy of using Prismocitrate 18 in achieving appropriate anticoagulation through assessments of systemic and post-filter blood ionized calcium (iCa) concentrations,
- evaluate the efficacy of using Prismocitrate 18 in delivering the prescribed CRRT dose, with delivered dose based on total (daily) effluent volume and expressed as mL/kg/hour,
- evaluate the safety profile of Prismocitrate 18 through assessments of metabolic parameters (including serum bicarbonate, iCa, total calcium, total calcium/iCa ratio, magnesium, chloride, and other relevant serum electrolytes); anion gap, pH, base excess, bleeding events (number, location, duration); and the number and type of blood transfusions along with the number of units infused, and
- complete training on administration of Prismocitrate 18 and demonstrate the understanding of the user groups on how to use the solution by passing an assessment at the end of training.

Study Design:
This study is a multi-center, prospective, non-blinded, one to one randomized study. A total of 160 adult patients, 80 in each study arm, will be enrolled at up to 15 investigational sites in the United States and Canada. Patients meeting all of the inclusion criteria and none of the exclusion criteria of this protocol and deemed treatable by either CRRT with Prismocitrate 18 solution or CRRT with no systemic anticoagulation are eligible for enrollment in the study. If a patient is receiving standard-of-care CRRT, they must be randomized within 24 hours of initiation of their standard-of-care CRRT. All patients will be treated with continuous venovenous hemodiafiltration (CVVHDF) as the study CRRT modality. Patients enrolled in the study will receive either Prismocitrate 18 anticoagulation or no systemic anticoagulation during their CRRT, and the extracorporeal circuit life will be monitored for up to 120 hours of study CRRT (Treatment Period). During the Treatment Period, the adequacy of anticoagulation in the Prismocitrate 18 patients will be assessed by monitoring extracorporeal circuit pressures and by assessment of systemic and post-filter blood iCa concentrations. Patients will be monitored for acid-base parameters and serum electrolytes at baseline (prior to any CRRT), initiation (after randomization but before the initiation of study CRRT), at initiation of study CRRT and at pre-determined intervals during treatment. Information on bleeding events (number, location, duration) and the number and type of blood transfusions along with the number of units infused will also be collected.

Study Population:
One hundred sixty (160) adult patients with AKI or other serious conditions who require CRRT are planned.

Inclusion/Exclusion Criteria:
Each patient must meet the following inclusion criteria to be enrolled in this study.

1. Patient or legally-authorized representative has signed a written informed consent form (ICF).
2. Patient must be receiving medical care in an intensive care unit (ICU) (eg, medical ICU, surgical ICU, cardiothoracic ICU, Trauma ICU, Mixed ICU, other).
3. Patient age ≥ 18 years.
4. Adult patients with AKI or other serious conditions who require treatment with CRRT.
5. Patients are expected to remain in the ICU and on CRRT for at least 72 hours after randomization.
6. Patients already receiving standard-of-care CRRT must be randomized within 24 hours of initiation of their standard-of-care CRRT.

Patients who meet any of the following exclusion criteria will not be enrolled in the study.

1. Patients requiring systemic anticoagulation with antithrombotic agents for reasons other than CRRT. The exception is patients receiving subcutaneous heparin for deep vein thrombosis prophylaxis according to institutional practice or patients on aspirin may be enrolled.
2. Patients in whom citrate anticoagulation is contraindicated such as patients with a known allergy to citrate or who have experienced adverse events associated with citrate products including patients with a prior history of citrate toxicity or patients with uncorrected severe hypocalcemia (whether in the context of current citrate administration or due to the underlying disease state).
3. Patients who are not candidates for CRRT.
4. Patients who are receiving extracorporeal membrane oxygenation (ECMO) therapy.
5. Patients with severe coagulopathy [ie, platelets < 30,000/mm3, international normalized ratio (INR) > 2, partial thromboplastin time (PTT) > 50 seconds] including severe thrombocytopenia (platelets < 30,000/mm^3), HIT (heparin induced thrombocytopenia), ITP (idiopathic thrombocytopenia purpura), and TTP (thrombotic thrombocytopenia purpura) should not be enrolled in the trial.
6. Patients with fulminant acute liver failure or acute on chronic liver failure as documented by a Child-Pugh Liver Failure Score > 10.
7. Patients with refractory shock associated with persistent, worsening lactic acidosis (lactate > 4 mmol/L). However, patients with improving subsequent serum lactate levels may be enrolled.
8. Patients unlikely to survive at least 72 hours.
9. Female patients who are pregnant, lactating, or planning to become pregnant during the study period. Note: A female patient of childbearing potential, defined as a woman less than 55 years old who has not had partial or full hysterectomy or oophorectomy, must have a negative serum beta human chorionic gonadotropin (β-hCG) pregnancy test during the screening period (after consent and prior to randomization) and before CRRT treatment begins. A female patient of childbearing potential must use medically acceptable means of contraception during their participation in the study.
10. Patients who are currently participating in another interventional clinical study.
11. Patients with a medical condition that may interfere with the study objectives.

Test Product, Dose, and Mode of Administration:
Prismocitrate 18 (the investigational drug) is intended to be used as a replacement solution for regional anticoagulation of the extracorporeal circuit in patients undergoing continuous renal replacement therapy (CRRT). The renal replacement solution for regional anticoagulation containing 18 mmol/L citrate is

designed for pre-dilution infusion into the extracorporeal circuit before the blood pump (target blood citrate concentration of 3 to 5 mmol/L of blood).

Study Duration:
The anticipated duration of the clinical trial is approximately 4 years from the first patient enrolled to the last patient complete.

Individual patients will participate in the study for up to 35 days with a study treatment period of up to 120 hours of study CRRT post-randomization. At the conclusion of study treatment, patient adverse events and serious adverse events will be collected for a period of 30-days.

Efficacy Assessments:
Primary Efficacy Endpoint:
The Prismaflex M150 Set extracorporeal circuit life will be assessed over a maximum of 120 hours by the duration of time for which each Prismaflex M150 Set can be used continuously over a maximum 72 hour timeperiod in each patient. The Prismaflex M150 Set will be replaced any time study CRRT is stopped during the Treatment Period (regardless of duration) or any time a circuit is used for 72 continuous hours (ie, "Advisory Time to Change Set"). The end of the extracorporeal circuit life will be defined by the occurrence of one or both of the following Prismaflex® System alarms/conditions if the alarms cannot be mitigated. At this point, study CRRT will be terminated and the extracorporeal circuit replaced because mitigation of the following alarms is not possible:

- “Warning: Filter Clotted” , and/or
- “Advisory TMP Too High”

Secondary Efficacy Endpoints:
Systemic and post-filter blood iCa concentrations will be assessed at baseline (systemic only), initiation (systemic only), 1 hour and every 6 hours during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period from the initiation of study CRRT in each patient as indications of both the extent of calcium chelation prior to the CRRT filter and calcium restoration after the CRRT filter. Post-filter iCa will only be measured in the Prismocitrate 18 arm.

Delivery of the prescribed CRRT dose will be based on the patient’s weight and daily recordings of the effluent volume (in mL). These data will be used to calculate delivered dose (mL/kg/hour).

Safety Assessments:
Safety endpoints include:

1. Serum bicarbonate and pH, will be measured at baseline, at initiation of study CRRT and every 6 hours from the initiation of study CRRT during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period.
2. Blood total calcium concentrations will be measured at baseline, at initiation of study CRRT 1 hour and every 6 hours from the initiation of study CRRT during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period from the initiation of study CRRT.
3. Serum electrolytes (sodium, potassium, chloride, phosphate, and magnesium) will be measured at baseline, at initiation of study CRRT and every 6 hours from the initiation of study CRRT during the 120 hour Treatment Period and at 120 hours or end of Treatment Period.
4. As indicators of citrate accumulation (along with pH), the total calcium/iCa ratio (both measurements in mmol/L) will be measured at baseline, at initiation of study CRRT, 1 hour and every 6 hours from the initiation of study CRRT during the 120 hour Treatment Period and at 120 hours or end of Treatment Period. Anion gap and base excess will be measured at baseline, at initiation of study CRRT and every 6 hours from the initiation of study CRRT during the 120 hour Treatment Period and at 120 hours or end of Treatment Period.
5. The number, location and duration of bleeding events during the 120 hour Treatment Period will be collected. If a blood transfusion is needed during the 120 hour Treatment Period, the number and type of transfusions along with the number of units infused will be collected.

6. Change from baseline to final measurement in laboratory and vital signs measurements will be collected.
7. The incidence of adverse events and serious adverse events from the time the patient signs the informed consent form (ICF) until 30-days post study CRRT treatment (end of study) will be collected.

Analysis of Training on Administration of Prismocitrate 18
The site level user groups will be trained on the use of Prismocitrate 18 in CRRT and their understanding assessed prior to use in the clinical trial setting. The user groups will be comprised of physicians, nurses, and other clinicians who may be part of prescribing, initiating, or modifying treatment during the 120 hour Treatment Period. A descriptive summary of training results on administration of Prismocitrate 18 will be provided in the Clinical Study Report following completion of the study.

Statistical Methods:
The Statistical Plan for the study can be found in Section 8.

Date of Original Approved Protocol: 2016 FEB 08

Date of Approved Amendment 1: 2016 MAY 20

Date of Approved Amendment 2: 2017 JAN 05

Date of Approved Amendment 3: 2018 FEB 08

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
ABG	arterial blood gases
ADR	adverse drug reaction
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
APACHE II	Acute Physiology and Chronic Health Evaluation II classification system
AST	aspartate transaminase
β-hCG	serum beta human chorionic gonadotropin
BFR	blood flow rate
BUN	blood urea nitrogen
Ca^{2+}	calcium
CFR	Code of Federal Regulations
CRRT	continuous renal replacement therapy
CT	computerized tomography
CTA	Clinical Trial Application
CVVHDF	continuous venovenous hemodiafiltration
DMC	data monitoring committee
eCRF	electronic case report form
EDC	electronic data capture
FA	full analysis set
FDA	Food and Drug Administration
g/dL	grams per deciliter
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPS	Global Patient Safety
[redacted]	[redacted]
HD	hemodialysis
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
iCa or iCa^{2+}	ionized calcium

ABBREVIATION	DEFINITION
ICU	intensive care unit
ICH	International Conference on Harmonization
IFU	Instructions For Use
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IV	intravenous
kg	kilogram
L	Liter
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalent
mg	milligram
mL	milliliter
mmHg	millimeter of mercury
mmol	millimole
MMRM	mixed-effects model repeated measures
mOsm	milliosmol
PBP	pre-blood pump
PI	principal investigator
PP	per protocol set
PT	prothrombin time
PTT	partial thromboplastin time
Q_B	blood flow rate (real blood flow pumped out of the patient)
Q_D	dialysate rate
Q_E	effluent rate
Q_{FR}	fluid removal rate
Q_{PBP}	pre-blood pump infusion rate
Q_R	replacement fluid rate
RCA	regional citrate anticoagulation
REB	research ethics board
RRT	renal replacement therapy
SAE	serious adverse event

ABBREVIATION	DEFINITION
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMP	transmembrane pressure (mmHg)
US	United States
VBG	venous blood gases

1. INTRODUCTION

1.1 Background and Rationale

Prismocitrate 18 Solution is an investigational new drug intended to be used as a replacement solution for regional anticoagulation of the extracorporeal circuit in patients undergoing continuous renal replacement therapy (CRRT). Prismocitrate 18 is a CRRT solution developed by Gambro AB (now part of Baxter Healthcare Corporation) for use as both a replacement solution and an anticoagulant to prevent clotting of the extracorporeal circuit. Regional citrate anticoagulation (RCA) has been in use for renal replacement therapy (RRT) since 1961 for conventional hemodialysis (HD) and for CRRT since 1990.[1,2] Multiple publications in the literature document the use of RCA in RRT and CRRT.[1-8] Recent meta-analyses of randomized controlled trials demonstrate benefits for RCA over standard heparin anticoagulation with respect to bleeding and circuit longevity in AKI patients treated with CRRT.[9-11]

The mechanism underlying the efficacy of citrate as an extracorporeal anticoagulant is chelation of calcium, an integral physiologic component of the clotting cascade. During CRRT with RCA, delivery of citrate to the “arterial” blood prior to the CRRT filter results in chelation of calcium, rendering blood passing through the filter effectively anticoagulated. After blood leaves the filter in the “venous” bloodline, the anticoagulant effect is reversed when the citrate containing blood is returned to the patient. The ionized calcium levels in the patient are maintained within normal levels by a calcium infusion. Due to the pivotal role played by calcium, frequent monitoring of both systemic (patient) and post-filter blood ionized calcium (iCa) concentrations is typically performed during RCA. Post-filter blood iCa concentration is considered an appropriate surrogate for assessing the level of anticoagulation achieved.

Continuous renal replacement therapy comprises several different therapies used primarily for the management of AKI patients. These therapies differ with respect to the primary mechanism for solute removal (ie, diffusion and/or convection). The modality to be applied in this trial will be continuous venovenous hemodiafiltration (CVVHDF) in which solute clearance occurs by both diffusion and convection, achieved by the use of dialysate and replacement fluid, respectively. Prismocitrate 18 will serve as a replacement and anticoagulation solution containing citrate as both an anticoagulant and buffer source, the latter being necessary for the treatment of metabolic acidosis that routinely accompanies AKI or other serious conditions.[12] In CVVHDF, use of a cleared bicarbonate-containing dialysate not only provides additional solute clearance but also specifically affords the capability to modulate acid-base balance with changes in dialysate flow rate or composition.

1.2 Benefits and Risks for the Study Population

Since RCA has been demonstrated in controlled trials to decrease the risk of bleeding in comparison to heparin, participating patients may benefit in this respect.[9,10] Moreover, the patient's participation may demonstrate clinical benefits associated with RCA's ability to increase delivery of the prescribed CRRT dose (relative to no anticoagulation).

Foreseeable risks for the patients receiving Prismocitrate 18 mainly pertain to the changes that may occur in electrolyte and acid-base balance in association with RCA. However, specific aspects of the protocol are designed to mitigate these risks. The main risk to the Control Group in which no anticoagulation will be used is shortened filter life due to filter and extracorporeal circuit clotting, potentially resulting in patient blood loss and a lower delivery of the prescribed dose of CRRT due to more frequent treatment interruptions.

Foreseeable risks related to the use of the Prismaflex® System for Prismocitrate 18 treatment include operational errors related to patient preparation, line or bag connections, machine settings, bag handling, and bag contents. These risks have been addressed within the study protocol, investigator brochure, operator manuals, and training. Additionally, these risks will be minimized with the inclusion of the training assessment secondary endpoint by which user groups will be trained on the use of Prismocitrate 18 in CRRT and their understanding will be assessed prior to their use of the Prismaflex® System for Prismocitrate 18 treatment in the clinical trial setting. These risks will undergo monitoring and mitigation activities throughout the duration of the study.

1.3 Study Sponsor

Gambro AB, the manufacturer of Prismocitrate 18, was acquired by Baxter Healthcare Corporation in 2013. Baxter Healthcare Corporation is the sponsor of this study.

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is to evaluate the efficacy of Prismocitrate 18 in prolonging extracorporeal circuit life in patients treated with CRRT. The Control Group will be patients receiving CRRT with no anticoagulation.

2.2 Secondary Objective(s)

The secondary objectives of this study are to evaluate the efficacy of Prismocitrate 18 in achieving appropriate anticoagulation through assessments of systemic and post-filter

blood iCa concentrations, and to evaluate the efficacy of using Prismocitrate 18 in delivering the prescribed CRRT dose, with delivered dose based on total (daily) effluent volume and expressed as mL/kg/hour. Additionally, the safety profile will be evaluated through assessments of metabolic parameters, including serum bicarbonate, pH, base excess, iCa, total calcium, magnesium, chloride, and other relevant serum electrolytes along with anion gap. The potential for the development of citrate accumulation will be evaluated specifically through assessments of the total calcium/iCa ratio (both measurements in mmol/L), anion gap and base excess (along with pH).[13] Finally, the potential for bleeding events (number, location, duration), and the number and type of blood transfusions along with the number of units infused will also be assessed.

From the functional perspective, another secondary objective is to complete training on administration of Prismocitrate 18 and demonstrate the understanding of the user groups on how to use the solution by passing an assessment at the end of training. The user groups who need to be assessed prior to use of Prismocitrate 18 in the clinical trial setting will be comprised of physicians, nurses, and other clinicians who may be part of prescribing, initiating, or modifying treatment during the 120 hour Treatment Period.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is a multi-center, prospective, non-blinded, one to one randomized study. A total of 160 adult patients, 80 in each study arm, will be enrolled at up to 15 investigational sites in the United States (US) and Canada. Patients meeting all of the inclusion criteria and none of the exclusion criteria of this protocol, and deemed treatable by either CRRT with Prismocitrate 18 solution or CRRT with no systemic anticoagulation, are eligible for enrollment in the study. If a patient is already receiving standard-of-care CRRT, they must be randomized within 24 hours of initiation of their standard-of-care CRRT. All patients will be treated with predilution CVVHDF as the study CRRT modality. Patients enrolled in the study will receive either Prismocitrate 18 anticoagulation or no systemic anticoagulation during their study CRRT, and extracorporeal circuit life will be monitored for up to 120 hours of study CRRT (Treatment Period). During the Treatment Period, the adequacy of anticoagulation in the Prismocitrate 18 patients will be assessed by monitoring extracorporeal circuit pressures and by assessment of systemic and post-filter blood iCa concentrations. Patients will be monitored for acid-base parameters and serum electrolytes at baseline prior to any CRRT), initiation (after randomization but before the initiation of study CRRT) and at pre-determined intervals during treatment. Information on bleeding events (number, location, duration) and the number and type of blood transfusions along with the number

of units infused will also be collected. During the Treatment Period, the patient will be monitored at baseline and as detailed in Section 7.

See Appendix 1, Blood Sampling Schedule and Appendix 2, Schedule of Events Table.

3.2 Rationale for Study Design and Control Group

During meetings with the US Food and Drug Administration (FDA) and with [redacted] both regulatory authorities determined the existing literature data are insufficient to support a New Drug Application/Submission and advised that a prospective clinical study was needed to demonstrate the effectiveness and safety of Prismocitrate 18. In the meetings with the FDA, an endpoint for an eventual clinical trial was clarified and it was agreed that extracorporeal circuit life would be considered an acceptable efficacy endpoint. Moreover, it was determined that the Control Group in the randomized controlled trial would receive no anticoagulation during CRRT. The decision to avoid systemic heparinization in the Control Group was based largely on recent controlled studies showing an increased bleeding risk with heparin anticoagulation (vs citrate) in CRRT patients.[3,4,6-8,14] This study will be performed under a FDA-authorized Investigational New Drug Application (IND).

This study will also be conducted at a study site(s) in Canada. For the Canadian site(s), this study will be performed under a [redacted]

3.3 Selection of Study Sites

This clinical trial will be conducted at up to 15 clinical trial sites in the US and Canada. The participating physicians, nurses and clinicians at these sites must have experience using citrate anticoagulation for CRRT with the Prismaflex device.

3.4 Study Duration

The anticipated duration of the clinical trial is approximately 4 years from the first patient enrolled to the last patient complete.

Individual patients will participate in the study for up to 35 days with a study treatment period of up to 120 hours of study CRRT post-randomization. At the conclusion of study treatment, patient adverse events and serious adverse events will be collected for a period of 30-days.

3.5 Study Product and Material

Prismocitrate 18 is an investigational CRRT solution developed by the Sponsor and provided to the participating sites for use as a replacement solution containing an

anticoagulant to prevent clotting of the extracorporeal circuit. All other solutions used for standard-of-care CRRT are to be provided by the investigational site.

Prismocitrate 18 Solution contains standard electrolytes (sodium and chloride) and citrate.

Table 1 shows Composition of Prismocitrate 18.

Table 1. Prismocitrate 18

Name of the Substance	Quantity for Prismocitrate 18 (g/L)
Sodium chloride	5.03
Sodium citrate	5.29
Composition	**Prismocitrate 18 (mmol/L)**
Citrate	18
Sodium	140
Chloride	86

Water for injections to 1,000 mL.
Hydrochloric acid for pH adjustment.
Theoretical Osmolarity=244 mOsm/L and pH≈7.4.

Prismocitrate 18 acts as both an anticoagulant for the extracorporeal circuit and a replacement solution to compensate for water and electrolytes removed in the filter effluent and achieve solute clearance through convection. Therefore, this solution would be indicated for continuous venovenous hemodiafiltration (CVVHDF). The pre-filter infusion rate of Prismocitrate 18 (based on its citrate concentration) is indexed to the blood flow rate (BFR) to achieve a target blood citrate concentration of 3 - 5 mmol/L of blood, manifested as a post-filter blood iCa concentration of < 0.4 mmol/L. Moreover, the rate of calcium reinfusion is guided by a target systemic blood iCa of 0.9 - 1.3 mmol/L. In the protocol, specific instructions regarding prescription adaptations to achieve these targets will be provided in Section 5.2.1.

In addition to its role as a replacement solution and anticoagulant, Prismocitrate 18 also is a buffer source through the metabolism of citrate to bicarbonate by the patient. Therefore, the prescription of Prismocitrate 18 is made according to the patient's fluid removal requirements, additional fluid inputs and outputs, and the desired acid-base and electrolyte balances. Moreover, Prismocitrate 18 is prescribed relative to the flow rates of the other therapeutic fluids used during CRRT (replacement fluid and/or dialysate). A

dedicated anticoagulation pump and infusion line, incorporated into the CRRT system and extracorporeal circuit, respectively, are required for the administration of Prismocitrate 18.

3.6 Commercial Product Provided by Sponsor

The Sponsor will loan each investigational site at least one Prismaflex System Control Unit with Version 7.xx Software. This loaner machine will be used with study patients only. An investigational site has the option to decline the loaner machine and use their institution's Prismaflex System Control Unit(s) with Version 7.xx Software. In addition, the Sponsor will provide each investigational site with commercially available Prismaflex M150 Sets for delivery of CRRT for all patients in the study (Prismocitrate Group and Control Group).

4. STUDY POPULATION SELECTION

4.1 Study Population

The study will include 160 adult patients with AKI or other serious conditions who require CRRT. These patients are critically ill and may require a legally-authorized representative to make medical decisions and provide informed consent on their behalf. Patients must meet all the inclusion criteria and not meet any of the exclusion criteria defined for this study.

4.2 Inclusion Criteria

Each patient must meet the following inclusion criteria to be enrolled in this study.

1. Patient, or legally-authorized representative, has signed a written informed consent form (ICF).
2. Patient must be receiving medical care in an intensive care unit (ICU) [eg, medical ICU, surgical ICU, cardiothoracic ICU, Trauma ICU, Mixed ICU, other].
3. Patient age ≥ 18 years.
4. Adult patients with AKI or other serious conditions who require treatment with CRRT.
5. Patients are expected to remain in the ICU and on CRRT for at least 72 hours after randomization.
6. Patients already receiving standard-of-care CRRT must be randomized within 24 hours of initiation of their standard-of-care CRRT.

4.3 Exclusion Criteria

Patients who meet any of the following exclusion criteria will be excluded from the study.

1. Patients requiring systemic anticoagulation with antithrombotic agents for reasons other than CRRT. The exception is patients receiving subcutaneous heparin for deep vein thrombosis prophylaxis according to institutional practice or patients on aspirin may be enrolled.
2. Patients in whom citrate anticoagulation is contraindicated such as patients with a known allergy to citrate or who have experienced adverse events associated with citrate products including patients with a prior history of citrate toxicity or patients with uncorrected severe hypocalcemia (whether in the context of current citrate administration or due to the underlying disease state).
3. Patients who are not candidates for CRRT.
4. Patients who are receiving extracorporeal membrane oxygenation (ECMO) therapy.
5. Patients with severe coagulopathy [ie, platelets < 30,000/mm^3, international normalized ratio (INR) > 2, partial thromboplastin time (PTT) > 50 seconds]; including severe thrombocytopenia (platelets < 30,000/mm^3), HIT (heparin induced thrombocytopenia), ITP (idiopathic thrombocytopenia purpura), and TTP (thrombotic thrombocytopenia purpura) should not be enrolled in the trial.
6. Patients with fulminant acute liver failure or acute on chronic liver failure as documented by a Child-Pugh Liver Failure Score > 10.
7. Patients with refractory shock associated with persistent, worsening lactic acidosis (lactate > 4 mmol/L). However, patients with improving subsequent serum lactate levels may be enrolled.
8. Patients unlikely to survive at least 72 hours.
9. Female patients who are pregnant, lactating, or planning to become pregnant during the study period. Note: A female patient of childbearing potential, defined as a woman less than 55 years old who has not had partial or full hysterectomy or oophorectomy, must have a negative serum beta human chorionic gonadotropin (β-hCG) pregnancy test during the screening period (after consent and prior to randomization) and before CRRT treatment begins. A female patient of

childbearing potential must use medically acceptable means of contraception during their participation in the study.

10. Patients who are currently participating in another interventional clinical study.
11. Patients with a medical condition that may interfere with the study objectives.

4.4 Removal of Patient from Therapy, Assessment, or Study

Patients are considered withdrawn/prematurely discontinued from the study if their participation is discontinued before completion of the required evaluations as specified in the protocol Section 6.5. However, only the patient's individual treatment will be interrupted and the study will continue. Patients may be withdrawn/prematurely discontinued from the study for any of the following reasons:

1. Adverse event (AE) or serious adverse event (SAE).
2. Protocol violation/deviation (ie, the patient failed to meet protocol entry criteria or did not adhere to the protocol requirements).
3. Pregnancy.
4. Voluntary withdrawal (ie, patient's request).
5. Termination of the study.
6. Investigator's discretion.
7. Death.
8. Other [with reason noted on the electronic case report form (eCRF)].

The Investigator may terminate a patient's study participation at any time during the study if he/she judges it to be in the patient's best interest. If a patient is withdrawn from the study, the Study Monitor must be informed in the shortest possible time, regardless of the reason for withdrawal. In addition, a patient may discontinue his or her participation at any time during the study. If a patient's participation is discontinued, the reason(s) must be recorded in the source documents and on the eCRFs. If a patient discontinues for any reason, every effort should be made to perform all of the procedures that are scheduled for the End of Treatment visit. Patients who are withdrawn from the study will not be replaced. In addition, all SAEs, related or not, will be followed post-study treatment period for 30 days and until stabilized, resolved, or returned to baseline.

The patient's individual treatment will be interrupted but the study will continue if an event occurs that is considered by the investigators and/or the Sponsor as possibly

leading to a deficiency in the patient's treatment and is related to the use of Prismocitrate 18.

4.5 Recruitment

Country level recruitment for the study will start in the US after FDA authorization of the IND and the Institutional Review Board (IRB) approvals at respective study sites and in Canada after [redacted] authorization of the CTA and the Research Ethics Board (REB) approvals at respective study sites.

Patients who meet the inclusion criteria will be clearly informed on the details of the study, including the potential benefits and risks to the patient prior to their enrollment in this study. The patient's consent must be documented via signature and date on the Patient ICF. Patients will be considered in screening for the study after the ICF has been signed. For patients who are unable to provide informed consent themselves, a legally-authorized representative consent is appropriate.

5. STUDY TREATMENT(S)

5.1 Enrollment

All patients who sign an ICF will be assigned a Subject ID number. Those patients who are confirmed to meet the inclusion/exclusion criteria will be considered enrolled patients. Enrolled patients will be randomized to one of two treatment arms (Prismocitrate Group or Control Group) in a 1:1 manner using a site-stratified central randomization scheme.

5.2 Treatment Administered

All patients in this study will be treated with the Prismaflex System Control Unit with Version 7.xx Software and the disposable Prismaflex M150 Set. The patients will be followed post-randomization for up to 120 hours from the initiation of study CRRT. This 120 hour post-randomization period will be referred to as the Treatment Period. At the time of randomization, if a patient is currently receiving CRRT, the standard-of-care CRRT extracorporeal circuit will be replaced with a new Prismaflex M150 Set. During the Treatment Period, patients will be treated up to 120 hours of study CRRT with either Prismocitrate 18 or no systemic anticoagulation. "Baseline" during the Treatment Period is defined as prior to any CRRT therapy, "Initiation" is defined as after randomization but before the initiation of study CRRT. Initiation may occur at the same time point as baseline, should enrollment and randomization occur prior to any CRRT therapy. Following data points will be collected during study CRRT for the duration of the Treatment Period:

- Extracorporeal circuit pressures will be measured and recorded by the Prismaflex System device in real time. The end of the extracorporeal circuit life will be defined by the occurrence of one or both of the following Prismaflex System alarms/conditions, if the alarms cannot be mitigated. At this point study CRRT will be terminated and the extracorporeal circuit replaced, because mitigation of the following alarms is not possible:
  - "Warning: Filter Clotted" , and/or
  - "Advisory TMP Too High"

  Note: The nurse at the clinical site will document the alarm and rationale to stop treatment on the eCRF. In addition, the Prismaflex logging information from the data cards (one card per patient) will be collected on an ongoing basis and anonymized data will be sent to Baxter for technical analysis. An Independent Adjudicator will make the final determination of the alarm cause (see Section 9.9 Primary Endpoint Adjudication).

- Serum bicarbonate and pH will be measured at baseline, initiation of study CRRT, at 6 hour intervals and at 120 hours or end of the Treatment Period (see Appendix 1).
- For measurement of delivered dose, daily effluent volume (in mL) will be recorded from the Prismaflex System history screen. In the Prismaflex software, the starting time for the charting interval will be set (eg, at 8:00 am) and the volumes and doses will be stored for each day starting at that time. The effluent volume together with the patient's weight will be used to calculate delivered dose (mL/kg/hour). Note that ***daily*** weight will need to be obtained and recorded/entered each morning (eg, at 8:00 am) in the "System Tools" screen for determination of both prescribed and delivered dose as part of standard clinical practice for each patient receiving CRRT.
- *For both study arms* - Systemic ionized blood calcium concentrations will be measured at baseline and initiation, 1 hour after initiation of CRRT (post-randomization) and then at 6 hour intervals up to 120 hours of CRRT (see Appendix 1).
  - For the Prismocitrate 18 Arm, the systemic ionized calcium must be measured 1 hour prior to the initiation of study CRRT. If initiation ionized calcium is less than 0.9 mmol/L, the investigator must correct the serum level to greater

than 0.9 mmol/L in order to begin CRRT. This corrected systemic ionized calcium will be considered the patient's initiation value (see Appendix 1).

- *For Prismocitrate 18 Arm Only* - Post-filter blood iCa will be measured 1 hour after initiation of CRRT (post-randomization) and then at 6 hour intervals up to 120 hours of CRRT (see Appendix 1).
- Blood total calcium concentrations will be measured at baseline, initiation, 1 hour and every 6 hours during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period from the initiation of study CRRT in each. In conjunction with simultaneous systemic iCa concentrations, the total calcium/iCa ratio (both measurements in mmol/L) will be determined (see Appendix 1).
- Serum electrolytes (sodium, potassium, chloride, phosphate, and magnesium, anion gap) and base excess will be measured at baseline, initiation and at 6 hour intervals of study CRRT (post-randomization) up to 120 hours (see Appendix 1).
- Blood urea nitrogen (BUN) and serum creatinine measurements will be measured at baseline, initiation and twice daily (post-randomization) up to 120 hours of study CRRT (see Appendix 1).
- Partial thromboplastin time (PTT), prothrombin time [(PT); PT/INR], hemoglobin/hematocrit and platelet count will be measured at baseline, initiation and at least once daily (post-randomization) up to 120 hours of study CRRT (see Appendix 1).
- Liver function tests are to be measured at baseline, initiation and then as determined by local standard-of-care (see Appendix 1).

During the Treatment Period, if a Prismaflex M150 Set clots or reaches an unacceptable circuit pressure as indicated by machine alarms/conditions, it will be replaced. The Prismaflex M150 Set will also be replaced after 72 hours of continuous use (ie, "Advisory Time to Change Set") or any time the patient (prior to 72 hours of use) must temporarily stop CRRT (eg, CT scan, etc.). In these cases, the filter set will be replaced before continuing CRRT.

Treatments will be performed according to this clinical protocol and in conjunction with the Operator's Manual for the Prismaflex System (Version 7.xx Software) and the Instructions for Use (IFU) for the Prismaflex M150 Set, respectively. Study sites, especially those who do not currently use the Prismaflex M150 Set, should carefully review the Prismaflex M150 Set IFU "Warnings" section #3 and "Hypersensitivity

Reactions" section as special attention must be paid to patients receiving ACE inhibitors and/or having already shown similar hypersensitivity reactions. The Principal Investigator (PI) or a trained healthcare professional must be present at all times during CRRT to immediately address and manage any clinical concerns or other issues. All recommendations and warnings mentioned in the Operator's Manual and IFU shall be strictly followed.

Recommendations for the initial flow rates in the experimental arm of Prismocitrate 18, post-dilution replacement solution, and dialysate are provided to the investigator (refer to Section 5.2.2.2). However, according to the clinical manifestations and needs of the patient, the local standard-of-care for CRRT may be instituted based upon the investigator's medical judgement. For the control arm, investigators are advised to use standard-of-care practices per their local institution. However, all such prescription data must be recorded on the eCRFs and adhere to the following general guidelines in both arms of the trial:

- Modality must be CVVHDF
- Minimum prescribed CVVHDF dose (based on total effluent volume) - 25 mL/kg/hour.
- Minimum BFR – 100 mL/minute.
- Experimental Arm - Maximum BFR – 200 mL/minute.
- Control Arm - Maximum BFR – 400 mL/minute. This maximum BFR allows centers to follow their local standard-of-care procedures related to higher BFR use in non-anticoagulated circuits
- Minimum post-filter replacement fluid rate of 200 mL/hour for de-aeration chamber
- Minimum pre-blood pump infusion of 1000 mL/hour (either citrate or replacement fluid depending on the study arm)

5.2.1 Cross-Over Patients

During the course of this clinical trial the assigned arms (Prismocitrate Group or Control Group) must be maintained for the duration of the study CRRT treatment if at all possible. Based on the controlled design of this study, the cross-over of patients is not allowed.

5.2.2 Study Arm Protocols

Participating investigator sites will use the following general guidelines for CRRT:

- Modality must be CVVHDF
- Minimum prescribed CVVHDF dose (based on total effluent volume) - 25 mL/kg/hour.
- Minimum BFR – 100 mL/minute.
- Experimental Arm - Maximum BFR – 200 mL/minute.
- Control Arm - Maximum BFR – 400 mL/minute. This maximum BFR allows centers to follow their local standard-of-care procedures related to higher BFR use in non-anticoagulated circuits
- Minimum post-filter replacement fluid rate of 200 mL/hour for de-aeration chamber
- Minimum pre-blood pump infusion of 1000 mL/hour (either citrate or replacement fluid depending on the study arm)

5.2.2.1 Initial Prescription Orders for Control Arm

For the control arm, investigators are advised to use the general guidelines listed in Section 5.2.2 in combination with the standard-of-care practices per their local institution.

5.2.2.2 Initial Prescription Orders for the Prismocitrate 18 Arm

This initial prescription only applies to patients randomized to the Prismocitrate 18 Arm.

- Blood Flow Rate (Q_B): 100 to 200 mL/minute.
- The anticoagulant/replacement solution to be used is Prismocitrate 18, which at final concentration will provide: 140 mmol/L sodium, 86 mmol/L chloride, 18 mmol/L citrate.
- Minimal Initial Flow rate (mL/hour) of Prismocitrate 18 (delivered from the Prismaflex System PBP scale by the PBP pump): 1000 mL/hour.
    - The flow rate can be titrated by 100 mL/hour increments to maintain post-filter blood iCa levels < 0.4 mmol/L.

Rinse and prime the Prismaflex M150 Set according to the IFU. No heparin containing solutions should be used for priming.

After the initial citrate protocol prescription, the general guidelines outlined in Section 5.2.2 should be followed.

5.2.2.2.1 Effluent Rate

Total effluent rate (Q_E) (mL/hour) = Pre-blood pump (PBP) infusion rate (Q_{PBP}) + Post-dilution replacement fluid rate (Q_R) + Dialysate rate (Q_D) + patient fluid removal rate (Q_{FR}).

- Q_{PBP} corresponds to the infusion rate of Prismocitrate 18.
- As specified in the Prismaflex M150 Set IFU, post-filter replacement fluid should be prescribed according to institutional practice for proper functioning of the de-aeration chamber. The use of a calcium-containing post-dilution solution is not recommended.
- To calculate the hourly effluent rate to be prescribed, assume the effluent rate is a surrogate for the daily CRRT dose and the minimum prescribed dose is 25 mL/kg/hour with a minimum target delivered dose of 20 mL/kg/hour per 24 hours dose of treatment for both groups.
- The required effluent rate (mL/hour) can then be calculated by multiplying the patient weight (in kg) at the time of CRRT initiation by the target prescribed dose.
- For example, a 90 kg patient would require a total effluent rate of 2,250 mL/hour (90 kg x 25 mL/kg per hour). While adjustments in the infusion rates of Prismocitrate 18, post-dilution replacement solution, and dialysate can be titrated to meet the desired metabolic and anticoagulation requirements for the patient, the total effluent rate should not appreciably change, with maintenance of a minimum prescribed dose of 25 mL/kg/hour.

5.2.2.2.2 Blood Flow Adjustments

Based on the anticoagulation and metabolic requirements of the patient, a change in BFR should prompt consideration of the need for concomitant changes in the citrate infusion, post-dilution replacement fluid, and dialysate rates (as described in Section 5.2.2.2.1).

5.2.2.2.3 Dialysate Fluid Orders

- Ensure the dialysate contains no calcium.

5.2.2.2.4 Calcium Fluid Orders

5.2.2.2.4.1 Calcium Gluconate Fluid Orders

Calcium gluconate, 38.75 mmol/L (1 amp: 4.65 mEq or 93 mg elemental calcium) in 500 mL of normal saline 0.9%; IV Infusion, 60 mL/hour. The actual calcium calculations applied will be based on current standard-of-care for patients receiving CRRT.

REQUIRED:

- Maintain systemic blood iCa levels between 0.9 and 1.3 mmol/L.
- Monitor blood iCa level 1 hour after initiation and then every 6 hours, and adjust as needed to maintain post-filter blood iCa < 0.4 mmol/L.
- Post-filter blood iCa levels can be measured from the post-filter blood sample port (blue in color) located on the return line of the Prismaflex M150 Set; this level can be used to guide the Prismocitrate infusion rate.
- Potassium, phosphorus, and magnesium should be replaced separately, as needed.

**Calcium infusion should stop if CRRT is stopped.

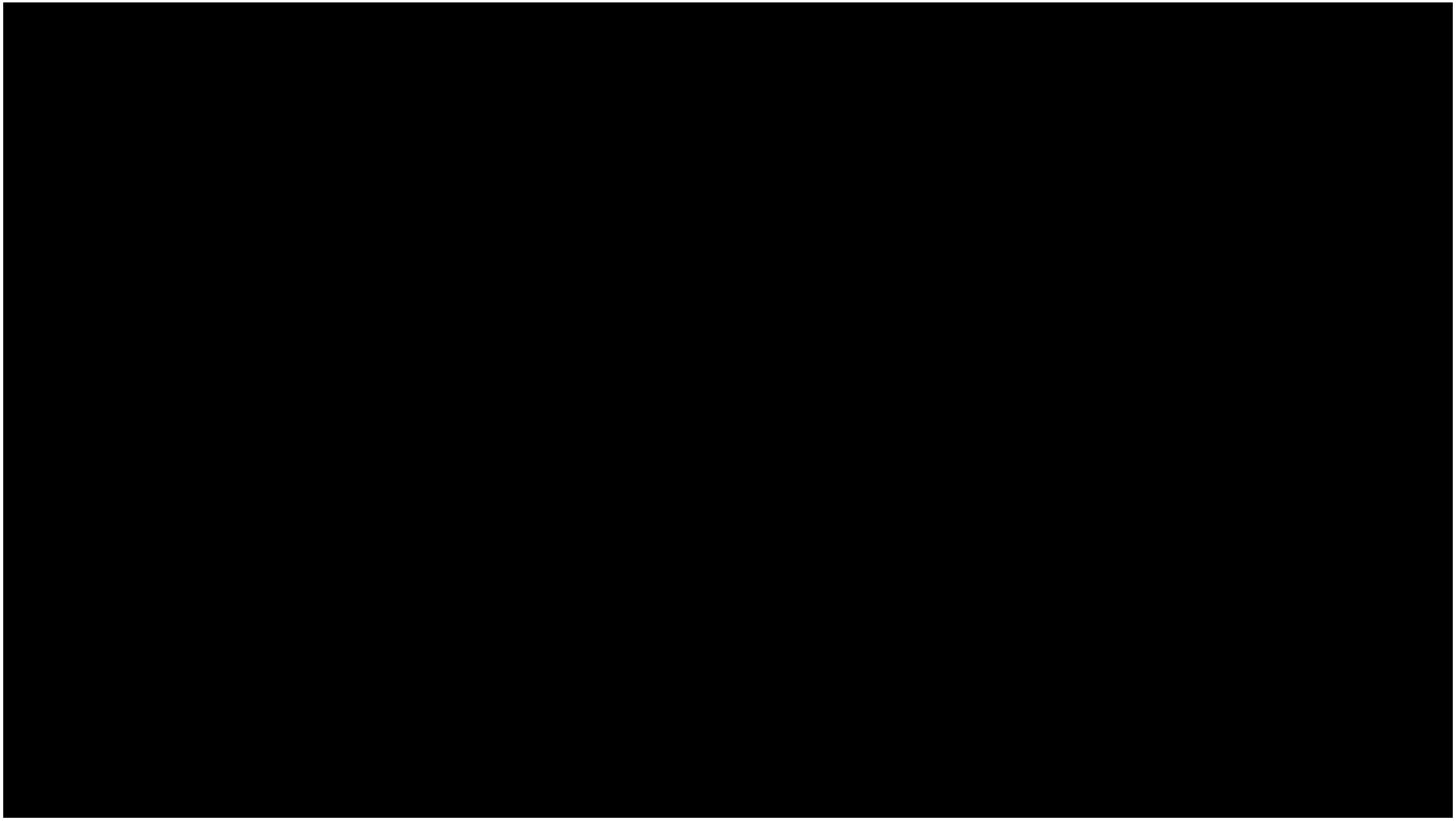
5.2.2.2.4.2 Calcium Chloride Fluid Orders

Calcium chloride 108.8 mEq in 1 L of normal saline 0.9% (note-total bag volume is 1080 mL); IV Infusion, 60 mL/hour. The actual calcium calculations applied will be based on current standard-of-care for patients receiving CRRT.

REQUIRED:

- Maintain systemic blood iCa levels between 0.9 and 1.3 mmol/L.
- Monitor blood iCa level from patient 1 hour after initiation and then every 6 hours, and adjust as needed to maintain post-filter blood iCa < 0.4 mmol/L.
- Post-filter blood iCa levels can be measured from the post-filter blood sample port (blue in color) located on the return line of the Prismaflex M150 Set; this level can be used to guide the Prismocitrate infusion rate.
- Potassium, phosphorus, and magnesium should be replaced separately, as needed.

**Calcium infusion should stop if CRRT is stopped.



5.2.2.3 Continuous Renal Replacement Therapy Dialysate

Sites will be instructed to use only commercially available standard CRRT sterile dialysate solutions having a density similar to saline solutions (close to 1) with the Prismaflex System. Dialysate formulation and flow rate are prescribed in accordance with the patient's clinical needs and each institution's standard clinical practice for CRRT.

For the Prismocitrate 18 Arm, the dialysate should have a bicarbonate concentration that accounts for the significant buffer load provided by Prismocitrate. Study sites will also ensure that the dialysate contains no calcium in the Prismocitrate 18 Arm.

5.2.2.4 Continuous Renal Replacement Therapy Replacement Fluids/Solutions

In the Prismocitrate 18 Arm, both Prismocitrate 18 and an intravenous-quality solution infused post-dilution will serve as the replacement fluids/solutions. Prismocitrate 18 will be delivered to the extracorporeal circuit by the Prismaflex System PBP via the PBP infusion line. The use of a calcium-containing post-dilution solution is not recommended in the Prismocitrate 18 Arm.

For the Control Group, replacement fluids (including one infused post-dilution) should be prescribed according to institutional practice at the investigative site.

5.2.2.5 Anticoagulants and Dosing/Administration of Prismocitrate 18

Either Prismocitrate 18 or no systemic anticoagulant will be used in this study. Prismocitrate 18 will be infused at a minimal initial rate of 1000 mL/hour. The rate will be titrated to maintain post-filter blood iCa levels < 0.4 mmol/L.

5.2.3 Monitoring of Therapy

Systemic iCa levels will be measured at baseline, initiation, and systemic and post-filter blood iCa levels will be measure 1 hour after initiation of study CRRT (post-randomization) and then every 6 hours thereafter and at 120 hours or end of Treatment Period. The pH and bicarbonate should be measured at baseline, initiation, and every 6 hours during the 120 hour Treatment Period and at 120 hours or end of Treatment Period. Health care professionals managing the patient should be instructed to notify the clinician immediately if the serum pH is < 7.20 or > 7.45, serum bicarbonate is < 15 or > 35 mmol/L, and/or the systemic blood iCa is < 0.9 or > 1.3 mmol/L.

Citrate metabolism may be impaired in patients with moderate to severe liver failure. The additional steps outlined below are needed to monitor specifically for the potential development of citrate accumulation, not only in these patients but in the entire study

population. Blood total calcium concentrations will be measured at baseline, initiation, 1 hour and every 6 hours during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period from the initiation of study CRRT. In conjunction with simultaneous systemic iCa concentrations, the total calcium/iCa ratio (both measurements in mmol/L) will be determined as an indicator of citrate accumulation and health care professionals managing the patient should be instructed to notify the clinician for any value above 2. 1. Moreover, based on the clinical judgement of the managing physician, this threshold value should also prompt an immediate CRRT prescription change designed to correct the metabolic disturbance. One of the following prescription changes should occur:

- Decrease in the Prismocitrate infusion rate; or
- Increase in the BFR; or
- Increase in the dialysate flow rate

The effect of one of these changes should be assessed with ongoing monitoring of relevant clinical and laboratory parameters - if improvement does not occur within two (2) hours, the Prismocitrate infusion should be stopped.

When a total calcium/iCa ratio of more than 2.1 is reported, any one of the following abnormalities reported concurrently should heighten the clinical suspicion of citrate accumulation and reinforce the need to undertake the steps outlined above:

- Decrease in iCa concentration to less than 1.1 mmol/L (despite adequate calcium compensation).Decrease in pH to value less than 7.20 or decrease in base excess (threshold value: -5 mmol/L).
- Increase in anion gap to more than 11 mmol/ L

Serum electrolytes (sodium, potassium, chloride, bicarbonate, phosphate, magnesium and anion gap) and base excess should be recorded at baseline, initiation, every 6 hours during the 120 hour Treatment Period and at 120 hours or end of Treatment Period. Coagulation parameters, hemoglobin, and hematocrit will be recorded at least once daily.

5.3 Selection and Timing of Dose for Each Patient

The timing and dose of the Prismocitrate infusion for the Prismocitrate Group will be prescribed and adjusted for each patient during the 120 hour Treatment Period per Section 5.2

5.4 Method of Assigning Patients to Treatment Groups

All enrolled subjects will be randomized to one of two treatment arms (Prismocitrate Group or Control Group) in a 1:1 manner using a site-stratified central randomization scheme.

5.5 Blinding

This is an open-label study that will not utilize blinding of the investigational drug. The study site team will be made aware of the treatment assignment at randomization. The study site team will be instructed to document the randomization assignment in source documents and follow their local procedure(s) to ensure their study patients receive their appropriate treatment.

5.6 Packaging and Labeling

For this clinical trial, investigational Prismocitrate 18 will be provided by the sponsor and will come packed in 5 L bags. All other solutions used in the management and care of patients in the trial will be provided by the local institution. Each bag will be labeled with a production lot number for product accountability.

Each Prismocitrate 18 product will be labeled according to local regulations. The US product will be labeled per Title 21 of the Code of Federal Regulations (CFR) Part 312.6 and Part 201. The Canadian product will be labeled per Part C, Division 5 of the Canadian Regulations.

All labels in the US will include the investigational statement:
"Caution: New Drug--Limited by Federal (or United States) law to investigational use."

All labels in Canada will include the investigational statement:
“CAUTION: New Drug – Limited by Federal Law to investigational use. To be used by qualified investigator only. Mise en garde: Nouveau medicament – Utilisation limitée à des fins de recherche par la loi fédérale. Doit être administer uniquement par des investigateurs qualifies.”

5.7 Storage and Accountability

All investigational drug and clinical supplies will be manufactured, handled, stored, and provided to patients in accordance with Good Manufacturing Practice (GMP) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP).

The investigators at each site will be supplied with the investigational product (IP), Prismocitrate 18, to be investigated during this clinical study. Prismocitrate 18 will be stored according to product label specifications, or other specific directions provided by the Sponsor.

Prismocitrate 18 must be stored in a locked area with restricted access. Prismocitrate 18 must only be used to treat patients enrolled in the study and randomized to the Prismocitrate Group under the sole supervision of the investigator.

The PI (or delegated person) at each site is solely responsible for keeping records of documents according to the following requirements:

- Date, quantity and lot numbers of Prismocitrate 18 units received by the investigator at the study site.
- Date, lot numbers and patient assignment of Prismocitrate 18 dispensed by the investigator.
- Lot numbers of damaged or destroyed Prismocitrate 18.

At each visit, the Study Monitor must ensure that the investigator has sufficient number of Prismocitrate 18 units at his/her disposition and that the Prismocitrate 18 is being used according to site requirements.

5.8 Investigational Product Destruction

If the IP, Prismocitrate 18, is determined to be unacceptable for initial or continued use, it shall be destroyed on site in accordance with the site's SOPs and replaced. The clinic coordinator will notify the Sponsor or its designee to arrange for delivery of replacement IP.

All IP will be reconciled and accounted for throughout the study. The study monitor will verify that all unused IP has been destroyed during the site close out visit. Additionally, at the conclusion of the study, records of all IPs delivery, inventory, dispensation, return, destruction, and disposition will be collected from the investigational site. If the investigational site procedures do not allow for IP destruction on site, the study monitor will arrange for the return of all unused IP.

6. STUDY PROCEDURES

6.1 Informed Consent

Patients or their legally-authorized representative will sign an ICF for the clinical study. As part of the consenting process, each ICF will be reviewed with the prospective study participants or their legal representatives, and an investigator will be available to answer questions regarding procedures, risks, and alternatives. The PI or his/her entitled designee will obtain a signed ICF from each patient or from the patient's legally-authorized representative or designee as defined by local law. Informed Consent Forms will be obtained before any protocol-specific procedures are performed.

The PI should allow the time necessary for the patient or the patient's legally-authorized representative to inquire about the details of the study after which the ICF must be signed and personally dated by the patient or by the patient's legally-authorized representative and by the person who conducted the informed consent discussion. The patient or a legally-authorized representative should receive a copy of the signed ICF and any other written information provided to the study patient. Only patients with the initial intention to complete the study should be considered for entry into the study.

The Sponsor will provide a template ICF which includes all GCP required elements. Preparation of the ICFs is the responsibility of the PI and must include all elements required by GCP and applicable regulatory requirements and must adhere to GCPs and to the ethical principles that have their origin in the Declaration of Helsinki. The language must be nontechnical and easily understood. All ICFs will be approved and reviewed by the Sponsor prior to IRB/REB review. The PI must furnish the Sponsor or its designee with a copy of each IRB/REB-approved ICF to be used in this study prior to the commencement of the study.

6.2 Medical History

Medical history relevant to the ICU admission for each patient will be obtained during Screening. Past and present conditions, as well as surgical procedures, will be recorded for the main body systems. Medication history will include all medications taken and/or prescribed during the 7-day window prior to informed consent and those relevant to ICU admission..

6.3 Physical Examination

Physical examinations will be obtained at the Screening and End of Treatment. Any new condition or worsening of a pre-existing condition from Screening will be noted and recorded on the AE eCRF page.

An attempt should be made to perform a final physical examination on patients who complete Screening and enroll, but who discontinue from the study early, particularly if the patient is discontinuing from the study because of an AE.

6.4 Vital Signs

Vital signs will include measurements of blood pressure, respiratory rate, temperature, and pulse rate. These vital signs will be obtained at Screening and at End of Treatment, with the exception of blood pressure which is collected at baseline (after randomization but before the initiation of study CRRT) and at 6 hour intervals during the Treatment Period, as well as at End of Treatment.

6.5 Clinical Laboratory Tests

6.5.1 Laboratory Parameters

Clinical laboratory tests are shown in Appendix 1.

6.5.2 Sample Collection, Storage, and Shipping

Sample collection is detailed in Appendix 1. All laboratory samples will be collected, stored, shipped and processed by local laboratories according to each site's procedures.

6.6 Dispensing Study Drug

Prismocitrate 18 must only be used to treat patients enrolled in the study and randomized to the Prismocitrate Group under the sole supervision of the PI. Study drug will be dispensed, recorded on source documents, and entered into eCRFs by site personnel as authorized by the PI.

6.7 Efficacy Variables

6.7.1 Primary Efficacy Endpoint

The Prismaflex M150 Set extracorporeal circuit life will be assessed as a time-to-event endpoint over a maximum 120 hours by the duration of time for which each Prismaflex M150 Set can be used continuously over a maximum 72 hour period in each patient. The Prismaflex M150 Set will be replaced any time CRRT is stopped during the Treatment Period (regardless of duration) or any time a circuit is used for 72 continuous hours (ie, "Advisory Time to Change Set"). The end of the extracorporeal circuit life will be defined by the occurrence of one or both of the following Prismaflex System alarms/conditions if the alarm cannot be mitigated. At this point, study CRRT will be terminated and the extracorporeal circuit replaced because mitigation of the following alarms is not possible:

- “Warning: Filter Clotted”, and/or
- "Advisory TMP Too High"

  Note: The nurse at the clinical site will document the alarm and rationale to stop treatment on the eCRF. In addition, the Prismaflex logging information from the data cards (one card per patient) will be collected on an ongoing basis and anonymized data will be sent to Baxter for technical analysis. An Independent Adjudicator will make the final determination of the alarm cause by examining the applicable historical electronic data available surrounding the alarm events (see Section 9.9 Primary Endpoint Adjudication).

The extracorporeal circuit life will be censored for cases where the Prismaflex M150 Set has been replaced for reasons other than reaching the end of the extracorporeal circuit life. Only filters for which the end of the extracorporeal circuit life was reached (ie, one or both Prismaflex System alarms/conditions occurred as defined above and alarm causes have been confirmed by an Independent Adjudicator) will be considered ‘events’ in terms of the statistical analysis.

6.7.2 Secondary Efficacy Endpoints

Systemic and post-filter blood iCa concentrations will be assessed at baseline (systemic only), initiation (systemic only), 1 hour and every 6 hours during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period from the initiation of study CRRT in each patient as indications of both the extent of calcium chelation prior to the CRRT filter and calcium restoration after the CRRT filter. Post-filter iCa will only be measured in the Prismocitrate 18 arm.

Delivery of the prescribed CRRT dose will be based on the patient’s weight and daily recordings of the effluent volume (in mL). These data will be used to calculate delivered dose (mL/kg/hour).

6.8 Safety Assessments

Safety endpoints include:

1. Serum bicarbonate and pH will be measured at baseline, initiation and every 6 hours during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period.

2. Blood total calcium concentrations will be measured at baseline, initiation, 1 hour and every 6 hours during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period from the initiation of study CRRT.
3. Serum electrolytes (sodium, potassium, chloride, phosphate, magnesium, and anion gap) and base excess will be measured at baseline, initiation and every 6 hours during the 120 hour Treatment Period and at 120 hours or end of Treatment Period.
4. As indicators of citrate accumulation (along with pH), the total calcium/iCa ratio (both measurements in mmol/L) will be measured at baseline, initiation, 1 hour and every 6 hours during the 120 hour Treatment Period and at 120 hours or end of Treatment Period, anion gap and base excess will be measured at baseline, initiation and every 6 hours during the 120 hour Treatment Period and at 120 hours or end of Treatment Period.
5. The number, location and duration of bleeding events during the 120 hour Treatment Period will be collected. If a blood transfusion is needed during the 120 hour Treatment Period, the number and type of transfusions along with the number of units infused will be collected.
6. Change from baseline to final measurement in laboratory and vital signs measurements will be collected.
7. The incidence of adverse events and serious adverse events from the time the patient signs the informed consent form (ICF) until the end of the study will be collected.

6.9 Analysis of Training on Administration of Prismocitrate 18

The end users who need to be assessed prior to use of Prismocitrate 18 in the clinical trial setting (as delegated by an investigator) will be comprised of physicians, nurses, and other clinicians who may be part of prescribing, initiating, or modifying treatment during the 120 hour Treatment Period. The assessment materials, 1407-004 Protocol Training Assessment 2015May26, are provided separate from the protocol through a secure access internet site. Additional assessment materials for specific end user groups may be provided as needed or as determined by an investigator. A descriptive summary of training results on administration of Prismocitrate 18 will be provided in the Clinical Study Report following completion of the study.

6.10 Adverse Events Assessments

An AE is any untoward medical occurrence in a patient or clinical investigational patient administered a study product, and that does not necessarily have a causal relationship with the treatment or drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory function), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), organ dysfunction (eg, cardiovascular failure, pancreatitis, etc.), systemic illness (eg, sepsis), or outcome of death temporally associated with the use of the study product, whether or not the event is considered associated with the study product.

- Laboratory and vital sign abnormalities qualify as AEs if medical intervention is required to treat or address the abnormality, if the patient must be discontinued from the study due to the abnormality, or if the value exceeds specific limits defined by the standard-of-care as qualifying it as an AE.
- An elective procedure/surgery that occurs during the course of a study, but is being performed for a documented pre-existing condition and was pre-planned prior to study entry will not qualify as an AE. If, however, the pre-existing condition unexpectedly deteriorates during the study requiring the procedure/surgery to be performed earlier than planned, the condition for which the procedure/surgery is being performed will qualify as an AE.

Adverse events will be collected starting from the time the patient signs the ICF until 30-days post study treatment period (end of the study). During the course of the study, the Investigator or designee shall monitor each patient for the occurrence of any AE. If an AE occurs, a full description of the event should be recorded including the date of onset, severity, time course, description, actions taken, and causal relationship of the AE to the study product(s). Investigators should review and reference the Causality definitions located in Section 6.10.1 when determining the relationship of the AE to the study product. The investigators may also discuss the event(s) with the Baxter Medical Monitor, but the Investigator must make, document and report the relationship for every AE. All AEs must be documented in source documents and on the eCRFs, no matter how common they are for a particular patient and regardless of the causality assigned by the Investigator.

All AEs and SAEs, regardless of relatedness, should be actively solicited and recorded by the Investigator or designee throughout the course of the study. Additionally, any AE voluntarily reported by the patient should be recorded and verified by the Investigator or

designee on the appropriate source documents and eCRF pages. Each SAE will be documented on a separate SAE report form.

The outcome/resolution of all AEs and SAEs will be determined by the Investigator and documented on the AE eCRF and the SAE report form. Investigators will be instructed to follow all AEs/SAEs as follows: Unrelated AEs will be followed until resolution or until the end of the study whichever occurs first. Adverse drug effects (related AEs) and all SAEs (related or not) will be followed until resolution or stable, including following the patient after the end of the study if necessary. The outcome categories that can be chosen on the eCRF by the Investigator include: Fatal, Not recovered/Not resolved (this outcome is reached for AEs which are ongoing when the patient's end of study is due to death related to another AE), Recovering/Resolving (this outcome is reached for AEs which are ongoing at the patient's end of study), Recovered/Resolved with Sequelae (if there are some residual effects caused by the event), Recovered/Resolved, and Unknown.

All SAEs regardless of their relationship to the study product will be submitted to Baxter by the Investigator or designee within 24 hours of becoming aware of the event.

An AE can result from the use of the study product in accordance with the protocol, as well as from an accidental or intentional misuse of the study product or any other treatment error such as unintentional administration or use of another product during the course of the study.

6.10.1 Definitions of Adverse Event Terms

Study Product:	Depending on the protocol, the term "study product" can mean the IP, the comparator product, or the blinded product.
Date of Onset:	The date that the signs and symptoms of the AE began.
Signs & Symptoms vs Diagnosis:	If a definitive diagnosis has been medically established by the physician caring for the patient or by the Investigator, this diagnosis should then be recorded as the AE. If a definitive diagnosis has not been medically established, the signs and symptoms should then be recorded as the AEs.
Diagnosis vs Complications	If a patient experiences not only a diagnosis, but additionally a complication of the diagnosis (ie, myocardial infarction with congestive heart failure), both the diagnosis and the medical complication should be collected and recorded as separate AEs on separate eCRFs.
Severity:	Severity will be assessed for each AE and defined using the following criteria: Mild – Is a transient discomfort and does not interfere in a significant manner with the patient's normal functioning level. The AE resolves spontaneously or may require minimal therapeutic intervention. Moderate – Produces limited impairment of function and can require therapeutic intervention, but produces no sequelae.

	Severe – Results in a marked impairment of function and can lead to temporary inability to resume usual life pattern. The AE produces sequelae requiring (prolonged) therapeutic intervention.
Causality:	Causality Assessment – A determination is made by the Investigator and sponsor as to whether there is a reasonable possibility that the device or drug is etiologically related to/associated with the AE. Causality assessment includes, for example, assessment of temporal relationships, association (or lack of association) with underlying disease, treatment association (or lack of association), presence (or absence) of a more likely cause, and physiologic plausibility. Categories for causality assessment are "probably associated," "possibly associated," "unlikely associated" and "not associated." Probably Associated: An AE follows a strong temporal relationship to the device or drug, and another etiology is unlikely or significantly less likely. Possibly Associated: An AE follows a reasonable temporal relationship to the device or drug, and an alternative etiology is equally or less likely compared to the potential relationship to the device or drug. Unlikely Associated: An AE has little or no temporal relationship to the device or drug and/or a more likely alternative etiology exists. Not Associated: An AE that is due to underlying or concurrent illness, complications, concurrent treatments or effect of another concurrent drug/therapy and is not associated to the device or drug (ie, does not follow a reasonable temporal relationship to the use of the device or drug nor has a much more likely alternative etiology).

6.10.2 Serious Adverse Event (SAE)

The following criteria qualify an AE as an SAE:

Death:	An event resulting in death (including a fetal death).
Life-threatening:	In the opinion of the investigator, an event that would have resulted in immediate death if medical intervention had not been undertaken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	During this investigation, all patients will be hospitalized.
Prolongation of Hospitalization:	An event that prolongs the patient's stay in the hospital. By definition, this is a different event from the event that resulted in the hospitalization.
Congenital Abnormality:	An abnormality detected at or after birth in the offspring of a study patient.
Persistent or Significant Disability/Incapacity:	An event that substantially interferes with the patient's daily activities of living. This category is not intended to include events of relatively minor medical significance such as minor trauma, diarrhea, nausea, etc.
Important Medical Event:	A medically important event or reaction that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or requires intervention to prevent one of the other outcomes listed above. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse.
Abortion:	The spontaneous or induced termination of pregnancy (includes elective, induced, spontaneous and missed abortion, as well as miscarriage).

6.10.3 Adverse Drug Reaction

All noxious and unintended responses to a medicinal product that are related to any dose should be considered adverse drug reactions (ADR). The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

6.10.4 Unexpected Adverse Drug Reaction

An unexpected ADR is an adverse reaction for which the nature or severity is not consistent with the applicable product information.

6.10.5 Suspected Unexpected Serious Adverse Reaction

An AE suspected to have a causal relationship to an investigational or marketed drug and meeting criteria for seriousness and unexpectedness. Suspected Unexpected Serious Adverse Reactions (SUSARs) are also reportable for active comparator products, placebo, or the clinical study protocol itself (ie, events due to study procedures).

6.10.6 Adverse Events Related to Anticoagulation or CRRT

The anticipated adverse effects for this study have been identified in the list below.

- Air embolism
- Anemia
- Bleeding episodes
- Blood loss
- Bradycardia
- Cardiopulmonary arrest
- Coagulation of the dialyzer/extracorporeal circuit resulting in blood loss
- Cramping
- Disequilibrium syndrome
- Dizziness
- Electrolyte Imbalance
  - Hypercalcemia
  - Hypocalcemia
  - Hyperkalemia
  - Hypokalemia
  - Hypermagnesemia
  - Hypomagnesemia
  - Hypernatremia
  - Hyponatremia
  - Hyperphosphatemia
  - Hypophosphatemia
- Excessive weight loss or gain
- Filter or tubing set blood leak resulting in blood loss
- Fluid imbalance
- Hemolysis
- Hypersensitivity or Allergic Reactions “First Use Reaction”
- Hypertension

- Hypotension
- Hypothermia
- Hypervolemia
- Hypovolemia
- Infection
- Metabolic acidosis
- Metabolic alkalosis
- Nausea
- Pyrogenic Reaction
- Tachycardia
- Vomiting

6.11 Site Reporting Requirements

During the course of the study, the Investigator or designee will routinely monitor each patient for the occurrence of any AE/ADE. If an AE/ADE occurs, the Investigator or designee will complete the AE eCRF which includes the following:

a. Description of the event
b. Start and stop date of the event
c. Timing of the event
d. Seriousness of the event (yes, no)
e. Severity of the event (mild, moderate, or severe)
f. Causality of the event (related to treatment and/or related to the IP)
g. Outcome of the event (fatal, not recovered/not resolved, recovering/resolving, recovered/resolved with sequelae, recovered/resolved, and unknown)

All SAEs must be reported to the Baxter Global Patient Safety (GPS) within 24 hours of the Investigator or designee becoming aware of its occurrence. The initial 24-hour reporting requirement can be met by using either the electronic SAE eCRF or the paper SAE form. The informed site team member should also contact their site monitor by phone or email to notify him/her of the event. This requirement is irrespective of whether the AE is thought to be possibly related to the study product or not. After the initial 24-

hour reporting, both the Baxter electronic SAE eCRF and the paper SAE report form must be completed for all SAEs. The paper SAE report form is to include copies of documents (de-identified) requested within the form (if applicable). The paper SAE forms should be sent by email to:

[redacted]

Copy: [redacted]

In case this email is down, the site must notify GPS by fax: [redacted]. Once received, the SAE report will be reviewed for completeness and forwarded on to the Medical Monitor and Baxter Global Patient Safety within 1 calendar day of receipt.

Follow-up or new information about a SAE should be provided by the investigator/designee using the paper SAE form within 24 hours of becoming aware of the new information. If the follow-up or new information impacts any of the fields in the electronic SAE eCRF the SAE eCRF should be updated within 24 hours of becoming aware of the new information.

If the Investigator suspects the SAE could possibly be a SUSAR, the following should also be contacted as soon as possible:

[redacted]**:**
[redacted], MD
[redacted]
Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, IL 60015
Tel: [redacted]
Email: [redacted]

Other Contacts:
[redacted], MS
[redacted]
Baxter Healthcare Corporation
Mobile: [redacted]
Email: [redacted]

[redacted], BSN, RN [redacted]

Baxter Healthcare Corporation
One Baxter Parkway, DF5-1W / Deerfield, IL 60015
Tel: [redacted] / Mobile: [redacted]
Email: [redacted]

Serious Adverse Events will be reviewed and causality assessment will be completed by Baxter.

6.11.1 Sponsor to FDA/[redacted] and Investigator to IRB/Ethics Committee

Baxter will assess each SAE reported by the Investigator to determine if the SAE qualifies as an Expedited Report according to FDA and/or [redacted] criteria. Per regulations, Investigators will receive a letter from Baxter describing the SUSAR. The Investigator should file this letter within their Investigator Study Binder. Additionally, the Expedited Report letter should be submitted by the Investigator to their IRB/REB, as appropriate per FDA or [redacted] regulations.

6.12 Concomitant Therapy

The Investigator should review any additions or changes in concomitant therapy. All medications should be recorded in the source documents or equivalent. Prior medications, defined as those taken and/or prescribed during the 7 day window prior to informed consent and those relevant to ICU admission, will be recorded on the eCRF. Concomitant medications, including dose, frequency, start and stop dates, and indication for use, will be recorded on the eCRF throughout the study.

6.13 Restrictions

Diet, Patient Activity or Concomitant Medication restrictions are not noted.

Systemic heparin or other systemic anticoagulants are prohibited.

6.14 Treatment Compliance

The facility nurse will fill out a treatment record for each study treatment, including CRRT start time, stop time, etc. Data from that record will be transcribed and submitted on eCRFs.

7. STUDY ACTIVITIES

7.1 Training on the Administration of Prismocitrate 18

The clinical sites will be required to be current users of Prismaflex Device Platform and users of citrate as an anticoagulant for CRRT circuits. The end users at these sites are authorized to use of the CRRT machines and regional citrate anticoagulation at their

institutions. Additional training on the administration of Prismocitrate 18 will be provided by the Sponsor. At the completion of training the site investigator and other end users (as delegated by an investigator) will complete an Evaluation (refer to 1407-004 Protocol Training Assessment 2015May26). Additional assessment materials for specific end user groups may be provided as needed or as determined by an investigator.

7.2 Consenting and Screening Period

Study procedures can only begin after the site has fully consented the subject. The data collection points listed in Section 7.3 will be collected during the screening period (after consent and prior to randomization). Subjects may screen up to 96 hours prior to randomization. It is anticipated that most study subjects will screen and randomize in a 24 hour period.

If any of the data points listed in Section 7.3 were collected prior to consenting the subject (within 96 hours) as standard-of-care, the site staff may enter those data points from the patient's chart into the eCRFs. The exception is Clinical laboratory evaluations which must be within 24 hours.

7.3 Patient Information to be Collected Prior to Initiation of Treatment

The following data will be collected and recorded on the eCRFs for each patient prior to treatment.

1. Signed Patient Informed Consent Form.
2. Patient Identification Number as assigned by the system.
3. Inclusion/Exclusion Criteria.
4. Patient Demographics.
    a. Gender.
    b. Illness severity score using the Acute Physiology and Chronic Health Evaluation (APACHE II) classification system.[15,16]
    c. Chronological age.
    d. Body measurements: weight, height, BMI (kg/m^2).
    e. Race.
    f. Ethnicity.
5. Patient Medical Information.
    a. Indication for CRRT*.

* If Indication for CRRT is AKI, specify cause.

b. Known allergies.
c. Current medications and those prescribed during the 7-day window prior to informed consent and those relevant to ICU admission.
d. Medical history – past/present conditions as well as surgical procedures.
e. Physical examination.
f. Vital signs.
g. Clinical laboratory evaluations as specified in Appendix 1.

7.4 Treatment Period

The following data will be collected and recorded on the eCRFs for each patient following randomization.

7.4.1 Treatment Information

1. Date & time patient randomized and treatment arm.
2. Date & time study CRRT initiated and discontinued.
3. Prismaflex M150 Set to include:
   a. Sequential number for Prismaflex M150 Set.
   b. Date & time of installation.
   c. Date & time for start and end of study CRRT for each Prismaflex M150 Set.
   d. Prismaflex M150 Set lot number (Prismaflex M150 Set must be used).
4. Blood access information.
   a. Catheter-type, manufacturer, length & size.
   b. Catheter anatomical insertion location.
5. Prismaflex System serial number (to confirm that only Prismaflex System is used in this study).
6. Treatment Modality.
   a. Continuous venovenous hemodiafiltration (CVVHDF) confirmation.

7.4.2 Treatment Prescription – initial and all changes during Treatment Period

1. Patient fluid removal flow rate (mL/hour).

2. Post-filter replacement flow rate (mL/hour).
3. Blood flow rate (mL/minute).
4. Dialysate flow rate (mL/hour).
5. Prismocitrate 18 flow rate (mL/hour).
6. Calcium Gluconate or calcium chloride infusion details: dilution and rate (mL/hour).

7.4.3 Dialysate Used

1. Formulation.
2. Brand name/Manufacturer.

7.4.4 Replacement Solutions Used

1. Formulation.
2. Brand name/Manufacturer.

7.4.5 Priming Solution

1. Formulation.
2. Brand Name/Manufacturer.

7.4.6 Calcium Gluconate or Calcium Chloride

1. Formulation.
2. Brand name/Manufacturer.

7.4.7 Extracorporeal Circuit (Prismaflex M150 Set) Information

1. Reason (including date and time) for treatment termination (ie, clotting, increased TMP, patient required treatment/diagnostic tests external to ICU, device malfunction, etc).
2. Visual assessment of extracorporeal circuit at time of treatment termination due to:
    a. Clotting in the Prismaflex M150 Set (ie, clotting in filter and blood tubing),
    b. Clotting in the blood access device, or

c. Clotting in both the blood access device and the Prismaflex M150 Set.

3. Complications related to blood loss (bleeding or Prismaflex M150 Set clotting and replacement).
   a. Number, location and duration of any bleeding events.
   b. Estimated blood loss (mL).
   c. Transfusion type (whole blood, packed cells, etc.).
   d. Transfusion volume.
   e. Adverse events.

7.4.8 Anticoagulation Information

1. Prismocitrate 18 (volume of Prismocitrate 18 used), or
2. No systemic anticoagulant.

7.4.9 Patient Clotting Parameters

1. Prothrombin time/international normalized ratio.
2. Activated partial thromboplastin time.
3. Platelet count.
4. Post-filter iCa.
5. The number of iCa determinations (whether the patient is on Prismocitrate or not).

7.4.10 Treatment Blood Concentration Data – According to the Sampling Schedule in Appendix 1

1. Blood Urea Nitrogen (BUN).
2. Creatinine.
3. Serum bicarbonate, pH and base excess.
4. Hemoglobin and Hematocrit.
5. Blood sodium, potassium, chloride, iCa (systemic and post-filter), total calcium, phosphorus, and magnesium.
6. Total Ca/iCa ratio.
7. Anion gap.

8. Liver function tests (AST, ALT, ALP, Total Bilirubin) – based on local standard-of-care.

7.4.11 Fluid Balance and Hemodynamic Parameters

1. Total fluid input and output volume (including dialysate, replacement fluid, and effluent).
2. Daily patient weights recorded each morning (eg, 8:00 am) for calculation of delivered CRRT dose.
3. Post-treatment weight when study CRRT is terminated.
4. Blood pressure including mean arterial pressure at randomization and at 6 hour intervals (± 1 hour) up to End of Treatment or 120 hours of study CRRT post-randomization and at 120 hours or end of Evaluable Period.

7.5 End of Treatment or Early Termination Procedures

The following End of Treatment information will be collected and procedures or evaluations will be performed after completion of study CRRT during the Treatment Period (up to 120 hours of study CRRT):

- Physical exam including weight.
- Vital signs.
- Adverse events/serious adverse events (if not previously reported).
- Concomitant medications.
- Clinical laboratory evaluations as specified in Appendix 1.
- Bleeding events (if not previously reported).
- Transfusions (if not previously reported).
- Disposition post-study CRRT Treatment Period.

If a patient discontinues from the study prematurely, every attempt should be made to perform all of the End of Treatment procedures and evaluations. Upon exiting the study, the patient will be treated per standard-of-care, which may or may not include continued CRRT.

7.6 End of Study Procedures

After completion of study CRRT during the Treatment Period (up to 120 hours of study CRRT) AE/SAEs will be followed for a period of 30 days. All patients who complete up to 120 hours of study CRRT and the 30-day AE/SAE follow up period will successfully complete the study. Related AEs and SAEs will be followed post-study until resolution or stable.

8. PLANNED STATISTICAL METHODS

8.1 General Considerations

Unless otherwise specified, treatment effects will be evaluated on the basis of a 2-sided significance level of 0.050 (when rounded to 3 decimal places). Unless otherwise noted, all analyses will be performed using Statistical Analysis Software (SAS®), SAS/GRAPH® and SAS/STAT® software, Version 9.2 of SAS for Windows, copyright © 2002-2008 SAS Institute Inc., on a Microsoft Windows Server. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.[17]

Further details of the planned statistical methods presented below will be provided in the study statistical analysis plan (SAP). The purpose of the SAP is to further elaborate the statistical methods described in the protocol and to describe analysis conventions to guide the statistical programming work. The SAP will be drafted prior to enrollment of the first patient and will be finalized prior to database soft lock in accordance with Baxter standard operating procedures.

8.2 Determination of Sample Size

A sample size of 80 patients in each treatment group will provide > 90% power for assessing the equality of the extracorporeal circuit life between treatment groups using a two-sided clustered log-rank test with an overall alpha level of 0.050. This is based on the following assumptions: median circuit lives of [redacted] and [redacted], respectively in the Prismocitrate and Control group, [redacted] filters per patient (during the Treatment Period of 120 hours) in the Prismocitrate and Control group, respectively, [redacted] of subjects discontinuing therapy for reasons other than due to clotting of the circuit (ie, common exponential dropout rate of [redacted]), a single interim analysis when 50% of patients have completed treatment, and combination of results from the two study stages (prior to vs after interim analysis) using Fisher's combination test.[18]

8.3 Analysis Populations

The Full Analysis (FA) Set will include all randomized patients who received any study treatment for any period of time.

All analyses will be performed on the FA Set unless otherwise noted.

In addition to the FA Set, a Per Protocol (PP) Set will be used to check the robustness and validity of the primary analysis by repeating the analysis on the PP Set as a sensitivity analysis.

The PP Set defines a subset of the FA Set including patients who:

- fulfill all inclusion criteria.
- do not meet any of the exclusion criteria.
- were randomized and treated according to the randomization scheme.
- received at least 80% of their prescribed CRRT dose.
- do not have major protocol deviations that might impact the assessment of the primary endpoint (eg, mechanical malfunction of the machine).
- have available survival data for extracorporeal circuit life of at least one circuit (ie, time to occurrence of Prismaflex System alarms/conditions as outlined in Section 6.7.1 Primary Efficacy Endpoint and alarm cause determined and confirmed by Independent Adjudicator as outlined in Section 9.9 Primary Endpoint Adjudication, or censored circuit life if no system alarms/conditions occurred until the circuit was used for 72 continuous hours or if CRRT was stopped during the Treatment Period for reasons other than system alarms/conditions or if Independent Adjudicator did not confirm the alarm cause).

8.4 Demographics and Baseline Characteristics

Demographic data include illness severity score (APACHE II), age, gender, race, height, weight and body mass index (BMI) calculated as weight (kg)/height^2 (m), and ethnicity.

Other baseline/screening data include:

1. Underlying disease.
2. Known allergies.

3. Current medications and medications prescribed during the 7-day window prior to informed consent and those relevant to ICU admission.
4. General medical history; medical conditions or surgical procedures.
5. Vital signs including height, weight, blood pressure, pulse rate, temperature, and respiratory rate.
6. Physical exam.
7. Laboratory parameters, see Appendix 1.

Continuous variables will typically be summarized by treatment group using the number of subjects n, mean, standard deviation, minimum, median and maximum and a t-test or Wilcoxon rank sum test will be used to evaluate mean differences between groups, as applicable. Frequency and percentages will be provided for the categorical variables by treatment group and a Fisher's exact test will be used to evaluate differences between treatment groups.

Demographics and Baseline Characteristics will be summarized by randomized treatment group, and for the FA Set only.

8.5 Efficacy Endpoints

8.5.1 Primary Efficacy Endpoint

The primary endpoint of the study, extracorporeal circuit life, will be analyzed as a time-to-event endpoint (survival analysis).

In the statistical analysis extracorporeal circuit life of a filter that is replaced due to continuous use for 72 hours, will be censored. Likewise, filters that are in use when the end of the observation period of 120 hours is reached, will be censored at their current duration of usage at the end of the observation period. Filters that are replaced any time CRRT is stopped for reasons other than filter clotting (including drop-outs), will be censored at their current duration of usage. Only filters that are replaced due to filter clotting or excessive transmembrane pressure as indicated by one or both Prismaflex System alarms/conditions as defined under Section 6.7.1 Primary Efficacy Endpoint and for whom alarm causes have been confirmed by an Independent Adjudicator, will be considered ‘events’ in terms of the statistical analysis.

Each filter used during the 120 hours observation period or until treatment is finished will be included in the statistical analysis (several filters per patient).

Separate estimates per treatment group will be provided for the primary endpoint based on Kaplan-Meier methodology. Differences between treatment groups will be assessed using a clustered log-rank test in order to account for the potential dependence among extracorporeal circuit lives of the same patient.[19]

Analyses of the primary endpoint will be carried out on the FA Set based on the randomized treatment groups (intent-to-treat principle).

An interim analysis will be carried out after 50% of subjects completed treatment. Please refer to Section 8.8 for further details regarding the interim analysis.

The study will be stopped early due to overwhelming efficacy when a p value of < 0.0087 is observed using the clustered log-rank test at the interim analysis, see section 8.8 (critical value based on Bauer & Kohne procedure with no early stopping for futility). If $p \geq 0.0087$ and the study continues enrollment into a second stage, Fisher's combination test will be performed at the end of the study using a critical value of 0.0087 which guarantees that the overall type 1 error is controlled and preserved at a maximum of 0.05.[18]

The analysis of the primary endpoint will be repeated using the PP Set as a sensitivity analysis. In order to assess a potential impact of informative censoring on the primary efficacy analysis, a sensitivity analysis will be carried out on the FA Set using different assumptions for cases where therapy (ie, a filter) was discontinued for reasons other than circuit clotting. Further details will be provided in the SAP.

8.5.2 Secondary Efficacy Endpoints

A descriptive summary of systemic and post-filter blood iCa concentrations as assessed baseline (systemic only), initiation (systemic only), 1 hour and every 6 hours from the initiation of study CRRT during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period will be provided by treatment group. Post-filter blood iCa concentrations will only be presented for the Prismocitrate 18 Arm.

A mixed-effects model repeated measures (MMRM) analysis will be used to evaluate differences between treatment groups in the change from initiation of study CRRT in systemic iCa concentrations that are collected 1 hour and every 6 hours from the initiation of study CRRT during the 120 hours Treatment Period and at 120 hours or end of the Treatment Period. If justified, separate models will be carried out for patients who did and did not receive standard-of-care CRRT.

In addition, frequencies and percentages will be provided for systemic iCa < 1.1 mmol/L by time point and treatment group (threshold indicative of decrease in iCa despite adequate calcium compensation).

A descriptive summary of the daily delivered dose and overall delivered dose will be provided by treatment group. Differences between treatment groups in the percentage of overall prescribed dose actually administered will be assessed on a 5% significance level using a two-sided t-test or Wilcoxon rank sum test, as applicable. However, the statistical test will only be carried out conditional upon a significant test result for the primary endpoint at the time point of the interim analysis or final analysis. This hierarchical test procedure guarantees that the overall type 1 error is controlled and preserved at a maximum of 5%.

Secondary Efficacy Endpoints will be analyzed on the FA Set based on the randomized treatment groups (intent-to-treat principle).

8.6 Safety Endpoints

Analysis of safety endpoints will be carried out on the FA Set based on the actual treatment groups for the following parameters:

1. A MMRM analysis will be used to evaluate differences between treatment groups in the change from baseline in serum bicarbonate and pH that are collected every 6 hours from the initiation of study CRRT during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period. Frequencies and percentages will be provided for pH < 7.2 by time point and treatment group (thresholds indicative of metabolic acidosis).
2. A MMRM analysis will be used to evaluate differences between treatment groups in the change from baseline in blood total calcium concentrations that are assessed at 1 hour and every 6 hours from the initiation of study CRRT during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period.
3. A MMRM analysis will be used to evaluate differences between treatment groups in the change from baseline in serum electrolytes (sodium, potassium, chloride, phosphate, and magnesium) that are collected every 6 hours from the initiation of study CRRT during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period.

4. A descriptive summary of the total calcium/systemic iCa ratio as assessed at baseline, at initiation of study CRRT, 1 hour and every 6 hours from the initiation of study CRRT during the 120 hour Treatment Period and at 120 hours or end of the Treatment Period will be provided by treatment group. Frequencies and percentages will be provided for total calcium/systemic iCa ratio > 2.1 by time point and treatment group (threshold suggestive of citrate accumulation). Frequencies and percentages will be provided for anion gap > 11 mmol/L by time point and treatment group (threshold indicative of metabolic disturbance) as well as for base excess < -5 mmol/L.
5. A descriptive summary of the number, location, and duration of bleeding events along with the estimated blood loss during the 120 hour Treatment period will be provided by treatment group. The number and type of blood transfusion along with the number of units infused will also be summarized.
6. An analysis of covariance (ANCOVA) model will be used to evaluate differences between treatment groups in the change from baseline to final measurement in laboratory and vital signs measurements.
7. Adverse events will be mapped to a primary SOC and Preferred Term according to MedDRA and will be summarized.

8.7 Analysis of Training on Administration of Prismocitrate 18

A descriptive summary of proficient completion of training on the administration of Prismocitrate 18 will be provided.

8.8 Interim Analysis

A single interim analysis will be conducted when 50% of patients have completed treatment. The purpose of the interim analysis is to evaluate the primary efficacy endpoint for overwhelming efficacy, or the need to adjust the sample size. If the primary analysis yields a statistically significant test result ($p < 0.0087$, critical value for clustered log rank test based on Bauer & Kohne procedure with no early stopping for futility) on the FA Set, and if further no safety concern or other considerations require continuation of enrollment, the study will be stopped for overwhelming efficacy. Otherwise enrollment of subjects will continue and the whole statistical analysis as described in this document will be carried out at the end of the study using Fisher's combination test.[18] This approach guarantees that an overall type 1 error of 0.05 is preserved.

Sample size re-estimation at the interim analysis will be based on Fisher's criterion (Fisher's combination test). Simulation studies will be run utilizing the p value observed at the interim analysis (p1) and the initial assumptions for median survival times in the two treatment groups (in the Prismocitrate 18 and Control group). Re-assessment of the sample size will target a conditional power of 90% for rejecting the null hypothesis given the observed p value of the interim analysis.

9. ADMINISTRATIVE CONSIDERATIONS

9.1 Investigators and Study Administrative Structure

Investigators that will be participating in this study will be sent a copy of this protocol along with an appropriate supply of regulatory documents. Once this protocol and regulatory documents have been received by a given study site, the study site will be contacted by their Clinical Monitor to encourage the site to complete and return the forms to Baxter in an expeditious manner.

9.2 Institutional Review Board or Research Ethics Board Approval

The IRB/REB must be constituted according to the applicable local and national requirements of each participating location. The Sponsor or its designee will require documentation noting all names and titles of members who compose the respective IRB/REB. If any member of the IRB/REB has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

The Sponsor or its designee will supply relevant documents for PIs to submit to their respective IRB/REB for the review and approval of the protocol. The PI must submit to a central or local IRB/REB this protocol, the patient ICFs, and, if applicable, patient recruitment materials and/or advertisements. Written approval by the IRB/REB of the protocol and ICFs must be obtained and submitted to the Sponsor or its designee before commencement of the study (ie, before shipment of the study drug). The IRB/REB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, patient ICF) reviewed; and state the approval date.

Sites must adhere to all requirements stipulated by their respective IRB/REB. This includes notification to the IRB/REB regarding protocol amendments, updates to the ICFs, recruitment materials intended for viewing by patients, SAEs, unexpected AE reports, and updates regarding the ongoing review of the trial at intervals specified by the respective IRB/REB, and submission of final study reports and summaries to IRB/REB. All IRB/REB approvals and relevant documentation for these items must be transmitted to the Sponsor or its designee via the PI.

9.3 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the ethical and quality standards of good clinical practice (ICH E6) and all applicable regulatory requirements and laws.

The PI will provide all necessary information on the protocol and the study drug to all physicians, nurses, and other personnel who participate in this study under the PI's supervision and will discuss this material with them as needed, to ensure that they are fully informed regarding the conduct of the study and the potential effects of the study drug.

9.4 Compliance with Protocol and Protocol Amendments

The study must be conducted as described in this approved protocol. The PI should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/REB and the Sponsor or its designee, except where necessary to eliminate an immediate hazard(s) to study patients.

9.5 Patient Confidentiality

All patient information, medical records, and laboratory data will be kept confidential. Information and data may be discussed, analyzed, and reported. However, code numbers will identify the patient on the eCRFs and in any reports, and the patient's identity will be kept confidential.

9.5.1 HIPAA Authorization Procedures – US Sites Only

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the PI and must include all elements required by the Department of Health and Human Service's Privacy Rule. Prior to the beginning of the study, the PI must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form. The PI must provide the patient or legally-authorized representative with a copy of the HIPAA authorization form in the language in which the patient is most proficient. The language must be nontechnical and easily understood. The PI should allow the time necessary for the patient or the patient's legally-authorized representative to inquire about the details of the authorization. The HIPAA authorization must be signed and personally dated by the patient or by the patient's legally-authorized representative and by the person who obtained the authorization. The patient or legally-authorized representative should receive a copy of the HIPAA authorization form prior to the patient's participation in the trial.

9.5.2 Personal Health Information – Canadian Sites Only

A valid signed ICF, approved by the Sponsor and the REB, will be obtained from each study patient permitting disclosure of the individual's "personal health information" (as defined in the Personal Health Information Protection Act) as required by, and in accordance with, the study.

9.6 Study Monitoring

The sponsor team or designee will monitor the treatment data on site and remotely as part of safety management and clinical monitoring. Monitoring will occur at regularly scheduled intervals at the study site to allow for verification by sampling of source documents and comparing these with information recorded on the eCRFs. In addition, eCRFs will also be monitored remotely during the course of study participation. Full details on eCRF monitoring will be specified in the Clinical Operations Plan. If data discrepancies are noted, the electronic treatment data can be corrected in the clinical trial database via addenda, queries, source data clarification forms or an audit trail.

The PI or a designated member of the PI's staff must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the patient's records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The eCRFs must be completed prior to each visit and be made available to the monitor so that their accuracy and completeness may be checked.

The database will be housed on a physically and logically secure computer server maintained in accordance with written security policies. The electronic data capture (EDC) system meets approved established standards for the security of health information and is validated per 21 CFR Part 11. The system also meets the ICH guideline E6R1 and applicable [redacted] regulations regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained and adhere to both US and Canadian laws regarding patient data. Patient identifying information will not be included in the database, but must be maintained in a secure fashion at the Investigator site.

All eCRF and treatment file data correction documentation will be maintained in the EDC system's audit trail. System backups for data stored and records retention for the study data will be consistent with standard procedures.

9.7 Electronic Case Report Forms and Study Records

All patient medical records will be kept strictly confidential. Personally identifiable information will not be transmitted to the Sponsor, or its designee, or to any third parties. Patient eCRFs will only be released to the Sponsor, or its designee(s), and to appropriate government agencies. Code numbers will be used to identify the patient on eCRFs and other study-related documents.

The PI is required to prepare and maintain adequate and accurate case histories for each patient. Source data will be transcribed on to eCRFs by the site designee. Transcribed data should accurately reflect the data recorded in the source documents. All pages of the eCRF must be reviewed by the PI and he/she will sign off on the eCRF book to verify that the data is accurate, complete, and reflects the source documentation. This review and sign-off may be delegated to a qualified physician appointed as a Sub-Investigator by the PI. The PI must retain a copy of the eCRFs, including records of any changes or corrections.

9.8 Data Monitoring Committee

This study will be monitored by a Data Monitoring Committee (DMC). The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. The DMC can stop a trial if it finds toxicities or if treatment is proven to be not beneficial. For this study, the DMC will include recognized experts in the field of dialysis clinical care and research who are not involved in this study.

The DMC will be responsible for monitoring safety at regular intervals throughout the study. The meeting schedule, frequency of data delivery, and data required will be at the discretion of the DMC to be defined by the elected DMC members. The Sponsor will notify the DMC when any subject experiences a related SAE. Additionally, at the discretion of the sponsor, the sponsor may call a meeting of the DMC for any other safety issues or at any time to review the safety of the protocol or IP(s). The DMC may, at any time, request additional information from the Sponsor.

9.9 Primary Endpoint Adjudication

An Independent Adjudicator highly experienced in administering CRRT to patients and in operating the Prismaflex machine will review eCRF data, alarm data (ie, alarm name as described in Section 6.7.1 Primary Efficacy Endpoint of this protocol) and the outcome of a Baxter technical analysis (eg, technical root cause for alarm: yes/no). The Independent Adjudicator will make the final determination of the alarm cause by

examining the applicable historical electronic data available surrounding the alarm events. The Independent Adjudicator will be blinded to the treatment assignment as well as to any potential information that might reveal a subject's treatment assignment. In the event that the Independent Adjudicator becomes unblinded, a new Independent Adjudicator will adjudicate the case once the information that revealed the treatment assignment is removed.

9.10 Protocol Violations/Deviations

Protocol violations/deviations will be documented in source and in the investigator's research study files as applicable. The clinical team will review deviations at a study level on a regular basis for issue trending and resolution.

9.11 Access to Source Documentation

Representatives of the Sponsor, or its designee, must be allowed to visit the study site regularly to assess the data quality and the integrity of the study. These representatives will review study records on site and directly compare these with the source documents, discuss the conduct of the study with the PI, and verify that the facilities remain acceptable. In addition, the study may be evaluated by the Sponsor's internal auditors or a designee, and/or by government inspectors, who must be allowed access to eCRFs, source documents, and other study files.

9.12 Data Generation and Analysis

Web-based electronic data entry must be completed for all patients enrolled in the study. The electronic data entry will be the responsibility of the investigator. The database will be maintained by Baxter.

Electronic Investigator signatures will be used to attest to the accuracy of data entered into the EDC system. Modifications to the data made by the investigator or his/her delegated assistants will be tracked in an audit trail within the EDC.

The Study Monitor, in collaboration with the investigators, must ensure that data entered into the EDC system are correct. Data editing for correction or clarification purposes must be done before the eCRFs have been transmitted for data processing and analysis. Subsequent corrections must be checked in writing and validated in signing by the investigators.

The investigators must ensure that they are accessible to the Study Monitor, the Study Manager or any authorized people at any time during the course of the study.

Data management will be carried out by the Baxter Clinical Development & Operations or assigned designee.

Baxter or assigned designee is responsible for the creation of the study eCRF and the associated electronic study database. Queries will be issued through the EDC in order to solve questions regarding missing data and coherence.

9.13 Retention of Data

The PI must retain all study records including IP disposition records, and source documents for the maximum period required by applicable regulations and guidelines or institution procedures or for the period specified by Baxter, whichever is longer. The PI must contact the Sponsor before destroying any records associated with the study. The Sponsor or its designee will notify the PI when the trial records are no longer needed. If the PI withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another PI, IRB). Baxter will be notified in writing of any such transfer.

9.14 Audits and Inspections

In addition to the routine monitoring procedures and in accordance with GCP principles, GCP audits might well be performed by the Quality Assurance members of Baxter.

These audits of clinical research activities are in accordance with applicable regulatory requirements, Baxter internal policies and procedures, to evaluate compliance with the principles of GCP.

An independent auditor (ie, Regulatory Authority, government agency, central Ethics Committee) may also wish to conduct an inspection (during the study or even after its completion). Full consultation with appropriate personnel will be made prior to and during such audit. The PI must be available during the audit. If an independent auditor requests an inspection, the PI will contact their Site Monitor, Study Manager, and Medical Director immediately.

9.15 Financial Disclosure

In 2001, the FDA issued a guidance document entitled “Financial Disclosure by Clinical Investigators” which provides guidance to industry on its final rule on financial disclosure that became effective 02 February 1999 and was published as Title 21 CFR Part 54.[20] This rule applies to all Investigators participating in clinical studies to be submitted to the FDA in support of an application for market approval. The

financial disclosure statement must be updated annually during the course of the study and for 1 year after the completion of the study.

According to the guidance, disclosable financial arrangements are defined as the following:

- Compensation made to the Investigator in which the value of compensation could be affected by study outcome.
- A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- Any equity interest in the Sponsor of a covered study (ie, any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices).
- An equity interest in a publicly held company that exceeds $50,000 in value.
- Significant payments of other sorts, which are payments that have a cumulative monetary value of $25,000 or more made by the Sponsor of a covered study to the Investigator or the Investigators institution to support activities of the Investigator exclusive of the costs of conducting the clinical study or other clinical studies, (eg, a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation, or honoraria) during the time the clinical Investigator is carrying out the study and for 1 year after completion of the study.

The intent of this regulation is to ensure the proper identification and disclosure of financial interests of clinical Investigators that could affect the reliability of data submitted to the FDA in support of a market application. Companies must meet these financial disclosure requirements, and failure to do so may result in the refusal by the FDA to accept an application for market approval of the product.

9.16 Publication and Disclosure Policy

Any information shared by the Sponsor regarding this study, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this clinical study are the property of the Sponsor. These data may be used by the Sponsor, now and in the future, for presentation or publication at the Sponsor’s discretion or for submission to regulatory agencies. In addition, the Sponsor

reserves the right of prior review and approval of data from this study relative to the potential release of proprietary information to any publication or for any presentation.

10. REFERENCE LIST

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Appendix 1 Blood Sampling Schedule

Parameter	Before Randomization	After Randomization But Before Initiation of Study CRRT[a]	During Study CRRT[b]	End of Study CRRT During Treatment Period
Complete Blood Count (CBC) and blood lactate measurement	Screening			
pH and base excess (ABG or VBG)		Baseline and Initiation	At 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, & 120 hours[b]	When Study CRRT is terminated
Serum bicarbonate		Baseline and Initiation	At 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, & 120 hours[b]	When Study CRRT is terminated
Systemic iCa^{2+}		Baseline, 1 hour prior to initiation of Study CRRT	At 1, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, & 120 hours[b]	When Study CRRT is terminated
Post-Filter iCa^{2+} Prismocitrate 18 Arm Only			At 1, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, & 120 hours[b]	When Study CRRT is terminated
Serum Electrolytes: Sodium, Potassium, Chloride, Phosphate, Magnesium, & Anion Gap		Baseline and Initiation	At 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 72, 78, 84, 90, 96, 102, 108, 114, & 120 hours[b]	When Study CRRT is terminated

Parameter	Before Randomization	After Randomization But Before Initiation of Study CRRT[a]	During Study CRRT[b]	End of Study CRRT During Treatment Period
Creatinine & BUN		Baseline and Initiation	Twice daily	When Study CRRT is terminated
Bleeding Parameters: PT/INR, PTT, hemoglobin, hematocrit, platelet count	Screening	Baseline and Initiation	At least once daily	When Study CRRT is terminated
Blood total calcium Total calcium/iCa^{2+} ratio	Screening	Baseline and Initiation	At 1, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 72, 78, 84, 90, 96, 102, 108, 114, & 120 hours[b]	When Study CRRT is terminated

Parameter	Before Randomization	After Randomization But Before Initiation of Study CRRT[a]	During Study CRRT[b]	End of Study CRRT During Treatment Period
Liver function tests (Alanine transaminase [ALT], Aspartate transaminase [AST], Alkaline phosphatase [ALP] and total bilirubin	Screening	Baseline	As determined by local standard-of-care	As determined by local standard-of-care

ABG=arterial blood gases; ALT=alanine transaminase; AST=aspartate transaminase; ALP=alkaline phosphatase; CBC=complete blood count; CRRT=continuous renal replacement therapy; iCa2+=ionized calcium; BUN=blood urea nitrogen, PT=prothrombin time; INR=international normalized ratio; PTT=partial thromboplastin time; VBG=venous blood gases

a If patient has not been on standard-of-care CRRT, the Baseline and Initiation labs are the same. If patient has been on standard-of-care CRRT for < 24 hours the Baseline labs are those collected prior to the standard-of-care CRRT with exception of systemic iCa2+, which blood must be drawn 1 hour prior to initiation of Study CRRT. For Baseline Labs the acceptable blood draw window is - 24 hours. For Initiation Labs, the acceptable blood draw window is ± 1 hour.

b Acceptable blood draw window for Serum bicarbonate, pH, Systemic & Post-Filter iCa2+, Blood total calcium, Total calcium/ iCa^{2+} ratio and Serum electrolytes (sodium, potassium, chloride, phosphate, magnesium, anion gap and base excess) is ± 1 hour.

Appendix 2 Schedule of Events

Evaluation	Screening and Baseline	During Study CRRT Treatment Period	End of Study CRRT During Treatment Period
Informed Consent	X		
Demographics, Medical and Medication Histories[a]	X		
Physical Examination	X		X
Height and BMI	X		
Weight[b]	X	X	X
Vital Signs	X		X
Randomization[c]	X		
Prismaflex System information[d]		X	
Prismaflex M150 Set information and extracorporeal circuit assessment[e]		X	
Blood access information[f]		X	
CRRT treatment modality[g]		X	
CRRT treatment prescription[h]		X	
Priming Solution[i]		X	
Replacement solution prescription[i]		X	
Dialysate prescription[i]		X	
Anticoagulation information[j]		X	
Clinical laboratory evaluations[k]		X	X
Blood pressure and mean arterial pressure [l]	X	X	X

Evaluation	Screening and Baseline	During Study CRRT Treatment Period	End of Study CRRT During Treatment Period
Effluent volume (in mL)[m]		X	X
AEs/SAEs		X	X
Concomitant medications		X	X
Bleeding events [n]		X	
Transfusions[o]		X	
Patient Fluid Removal[p]		X	

[a] Demographics will include gender, illness severity score, chronological age at consent, pre-study CRRT weight and height. Medical history will include indication for CRRT, known allergies, past/present conditions as well as surgical procedures. Medication history will include all medications taken and/or prescribed during the 7-day window prior to informed consent and those relevant to ICU admission.

[b] In addition to the pre-study CRRT weight, during the treatment period, daily weight will need to be obtained and recorded/entered each morning (eg, at 8:00 am) in the "System Tools" screen.

[c] All enrolled subjects will be randomized to one of two treatment arms (Prismocitrate Group or Control Group) in a 1:1 manner using a central randomization scheme.

[d] Prismaflex System information will include collection of the Prismaflex System serial number as well as the date and time of study CRRT initiation and termination (each event over the 120 hour Treatment Period). This will include recording all disruptions in treatment (eg, circuit clotting, machine malfunction, patient required treatment/diagnostic tests external to ICU).

[e] Prismaflex M150 Set information will include the sequential set number, product lot number, date and time for installation and replacement, and the reason for replacement. The end of the extracorporeal circuit life will be defined by time at which one or both of the following Prismaflex System

alarms/conditions occur after which the study CRRT treatment will be terminated and the patient will end the treatment period if mitigation of the following alarms is not possible: “Warning: Filter Clotted” and/or "Advisory TMP Too High".

[f] Blood access information will include catheter-type, manufacturer, length & size, and catheter anatomical insertion location.

[g] CRRT treatment modality will be confirmed as CVVHDF (Hemodiafiltration).

[h] CRRT prescription will include patient fluid removal flow rate (mL/hour), post-filter replacement flow rate (mL/hour), PBP flow rate (mL/hour), BFR (mL/hour), dialysate flow rate (mL/hour), Prismocitrate 18 flow rate (mL/hour) and calcium gluconate or calcium chloride infusion details.

[i] Priming solution formulation, brand name/manufacturer; Dialysate and replacement solution prescription information will include the brand name/manufacturer, formulation, and volume. The initial prescription will be recorded along with any changes throughout the Treatment Period.

[j] Anticoagulation information will include confirmation if the patient was randomized to ‘Prismocitrate 18’ or ‘no systemic anticoagulation’.

[k] Clinical laboratory evaluations are presented in detail in Appendix 1.

[l] Blood pressure including mean arterial pressure is collected at baseline (after randomization but before the initiation of study CRRT) and at 6 hour intervals during the Treatment Period up to 120 hours of study CRRT, as well as at End of Treatment.

[m] Effluent volume (in mL) will be recorded from the Prismaflex System history screen. In the Prismaflex software, the starting time for the charting interval will be set (eg, at 8:00 am) and the volumes and doses will be stored for each day starting at that time.

[n] Bleeding events information will include number, location, duration, estimated blood loss, and adverse event data (if applicable).

[o] All blood transfusions information will include: (number, type, and number of units infused), relevant laboratory parameters (ie, hemoglobin/hematocrit and platelet values, etc.), as well as adverse event data (if applicable).

[p] Patient Fluid Removal data collection will include post-treatment weight, the amount of fluid removed, and administration of input therapeutic fluids.

Appendix 3 Investigator's Signature

Study Title:	Clinical Evaluation of Use of Prismocitrate 18 in Patients Undergoing Acute Continuous Renal Replacement Therapy (CRRT)
Study Number:	1407-004
Final Date:	2016 FEB 08
Amendment 1 Date Approved:	2016 MAY 20
Amendment 2 Date Approved:	2017 JAN 05
Amendment 3 Date Approved:	2018 FEB 08

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

<enter name and credentials>
<enter title>
<enter affiliation>
<enter address>
<enter phone number>