Statistical Analysis Plan: 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
Study Design	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 US and Canada.
Product Name:	Prismocitrate 18
Formulation/Indication:	A replacement solution indicated for regional anticoagulation of the extracorporeal circuit in patients undergoing continuous renal replacement therapy (CRRT)
Statistician:	[redacted] Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015 Tel: [redacted] Email: [redacted]
Sponsor:	Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015
Responsible Medical Officer:	[redacted], MD, PhD [redacted] Baxter Healthcare Corporation
Final Date:	26 JUN 2018
Version:	4.0

[redacted]

[redacted]

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1. SIGNATURE PAGE

Study Title:	Clinical Evaluation of Use of Prismocitrate 18 in Patients Undergoing Acute Continuous Renal Replacement Therapy (CRRT)
Study Number:	1407-004
Statistician:	[redacted]

I have read this statistical analysis plan and confirm that to the best of my knowledge it accurately describes the planned statistical analysis of the study.

Prepared by:_____ Date:_____

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Baxter Research & Development
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Approved by:__[redacted]__ Date:_____

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Approved by:__[redacted]__ Date:__[redacted]__

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
ABG	Arterial Blood Gases
AE	Adverse Event
AKI	Acute Kidney Injury
ANCOVA	Analysis of Covariance
APACHE II	Acute Physiology and Chronic Health Evaluation II Classification System
β-hCG	Serum Beta Human Chorionic Gonadotropin
BFR	Blood Flow Rate
BL	Baseline
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
Ca^{2+}	Calcium
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
CVVHDF	Continuous Venovenous Hemodiafiltration
ECMO	Extracorporeal Membrane Oxygenation
EOS	End of Study
EOT	End of CRRT During Evaluation Period
g/dL	Grams per Deciliter
HD	Hemodialysis
ICF	Informed Consent Form
iCa or iCa^{2+}	Ionized Calcium
ICU	Intensive Care Unit
INR	International Normalized Ratio
Kg	Kilogram
L	Liter
MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalent
mg	Milligram
mL	Milliliter
mmHg	Millimeter of Mercury

ABBREVIATION	DEFINITION
mmol	Millimole
MMRM	Mixed-Effects Model Repeated Measures
mOsm	Milliosmol
PBP	Pre-blood Pump
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
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
TMP	Transmembrane Pressure (mmhg)
US	United States

3. INTRODUCTION

This Statistical Analysis Plan is intended to describe the planned statistical analysis of study 1407-004.

3.1 Background and Rationale

Prismocitrate 18 Solution is intended to be used as a replacement solution for regional anticoagulation of the extracorporeal circuit in acute kidney injury (AKI) patients treated with 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[1] for conventional hemodialysis (HD) and for CRRT since 1990[2]. Multiple publications in the literature document the use of RCA in RRT and CRRT. 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. [3-8]

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 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.

4. TRIAL OBJECTIVES

4.1 Primary Objectives

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.

4.2 Secondary Objectives

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 assessment of the total calcium/iCa^{2+} ratio (both measurements in mmol/L), anion gap and base excess (along with pH). 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 hours evaluation period.

4.3 Exploratory Objectives

Not applicable.

5. STUDY DESIGN AND CONDUCT CONSIDERATIONS

5.1 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 (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.

5.1.1 Baseline Definition

Baseline (BL) will be defined as the last measurement before the initiation of CRRT. If a patient has not been on standard-of-care CRRT, the Baseline and Initiation labs will be the same. In this case, the acceptable baseline laboratory measurements can be up to 1 hour after initiation of CRRT.

5.2 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] in the Prismocitrate 18 and Control group, [redacted] filters per patient (during the Evaluation period of 120 hours) in the Prismocitrate 18 and Control group, [redacted] of subjects discontinuing therapy for reasons other than due to clotting of the circuit (i.e., 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[9].

5.3 Randomization Procedure

All enrolled subjects will be randomized to one of two treatment arms (Prismocitrate 18 or Control Group) in a 1:1 manner using a site-stratified central randomization scheme.

5.4 Schedule of Visits and Procedures

5.4.1 Schedule of Events

The schedule of events is presented below in Table 1.

Table 1 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
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	

Evaluation	Screening and Baseline	During Study CRRT Treatment Period	End of Study CRRT During Treatment Period

[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 hours 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 Table 2.

[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 (e.g., 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 (i.e., 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.

5.4.2 Schedule of Blood Sampling

The schedule of blood sampling is presented below in Table 2.

Table 2 Schedule of Blood Sampling

Parameter	Before Randomization	After Randomization but Before Initiation of Study CRRT[a]	During Study CRRT[b]	End of Study CRRT During Treatment Period[c]
Complete Blood Count (CBC) Blood Lactate Measurement	Screening			
pH 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
<u>Serum Electrolytes:</u> 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
Creatinine BUN		Baseline and Initiation	Twice Daily	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[c]
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
Liver Function Tests: Alanine Transaminase [ALT] Aspartate Transaminase [AST] Alkaline Phosphatase [ALP] 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; iCa^{2+}=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 iCa^{2+}, 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.

[c] If a parameter has not been measured when study CRRT was terminated, the last available measurement collected during the treatment period will be used as the end of study measurement

5.5 Efficacy Measures

5.5.1 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 hours 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 (i.e., "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, CRRT will be terminated and the extracorporeal circuit replaced:

- “Warning: Filter is 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 (for further details please see Section 9.9 Primary Endpoint Adjudication of study protocol).

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 (i.e., 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.

5.5.2 Secondary Efficacy Endpoints

Systemic and post-filter blood iCa concentrations will be assessed at baseline (systemic only), 1 hour and every 6 hours during the 120 hours Evaluation period and at 120 hours or end of the Evaluation period from the initiation of 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.

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

5.6 Safety Measures

1. Serum bicarbonate and pH will be measured at baseline and every 6 hours during the 120 hours Evaluation period and at 120 hours or end of the Evaluation period.
2. Blood total calcium concentrations will be measured at baseline, 1 hour and every 6 hours during the 120 hours evaluation period and at 120 hours or end of the Evaluation period from the initiation of CRRT.
3. Serum electrolytes (sodium, potassium, chloride, phosphate and, magnesium) will be measured at baseline and every 6 hours during the 120 hours evaluation period and at 120 hours or end of the evaluation period.
4. As indicators of citrate accumulation (along with pH), the total calcium/ iCa^{2+} ratio (both measurements in mmol/L) will be measured at baseline, 1 hour and every 6 hours during the 120 hours evaluation period and at 120 hours or end of evaluation period, anion gap and base excess will be measured at baseline and every 6 hours during the 120 hours evaluation period and at 120 hours or end of evaluation period.
5. The number, location and duration of bleeding events during the 120 hours Evaluation period will be collected. If a blood transfusion is needed during the 120 hours Evaluation 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 (AEs) and serious adverse events (SAEs) from the time the patient signs the informed consent form (ICF) until the end of the study will be collected.

5.7 Pharmacokinetic Parameters

Not applicable.

5.8 Other Parameters

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 hours Evaluation 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.

5.9 Completion and Discontinuation

The number of completed and discontinued subjects along with reasons for discontinuation will be summarized. Individual reasons for study discontinuation will be listed.

6. STUDY POPULATIONS

The following inclusion and exclusion criteria were applied in the selection of study patients:

Inclusion Criteria

1. Patient, or legally-authorized representative, has signed a written ICF.
2. Patient must be receiving medical care in an intensive care unit (ICU) [e.g., medical ICU, surgical ICU, cardiothoracic ICU, Trauma ICU, Mixed ICU, other].
3. Patient age $\geq$ 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.

Exclusion Criteria

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 [i.e., 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 (hereditary idiopathic 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.

6.1 Subject Disposition

The number of study patients included in the two (2) different analysis sets will be summarized by treatment group.

6.2 Analysis Populations

Statistical analyses will be carried out based on two (2) different analysis sets:

6.2.1 Full Analysis Set (FA)

The Full Analysis Set (FA) will include all randomized patients who received any study treatment for any period of time. The Full Analysis set will be analyzed based upon the subjects randomized treatment.

6.2.2 Per-Protocol Analysis Set (PP)

The Per-Protocol Analysis Set (PP) defines a subset of the FA 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 (e.g., mechanical malfunction of the machine)
- have available survival data for extracorporeal circuit life of at least one circuit (i.e., time to occurrence of Prismaflex System alarms/conditions as outlined in Section 5.5.1 Primary Efficacy Endpoint, 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 evaluation period for reasons other than system alarms/conditions).

The Per Protocol Set will be analyzed based upon the subjects randomized treatment.

6.3 Protocol Deviations

Protocol Deviations will be classified as major and minor deviations.

Subjects with any major protocol deviation that may impact the primary endpoints will be excluded from the per-protocol analysis set, including but not limited to the following:

- Violations of inclusion and/or exclusion criteria
- Use of prohibited medication known to influence the primary endpoint
- Randomization or treatment errors
- Improper administration of study product
- Improper assessment of the primary endpoint
- Any other protocol deviations that may impact the primary endpoints

Frequencies of protocol deviations will be presented by study site and across all study sites on a deviation as well as on a subject basis.

7. SUBGROUPS

No specific subgroup analyses are planned for this study.

8. STATISTICAL ANALYSIS

Unless specifically stated otherwise, throughout the document, Prismocitrate 18 relates to the study group receiving CRRT with Prismocitrate 18 solution whereas Control relates to the study group receiving CRRT with no systemic anticoagulation before a potential cross-over of treatments.

8.1 General/Types of Analyses

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). All analyses will be performed using Statistical Analysis Software (SAS®), SAS/GRAPH® and SAS/STAT® software, Version 9.2 of SAS for Windows, Copyright© 2018 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[10].

8.2 Handling of Missing Data

Missing data will neither be estimated nor replaced. No imputation of missing values will be performed. The survival type nature of data of the primary efficacy endpoint allows inclusion of any available information on extracorporeal circuit life in the statistical analysis according to the defined analysis populations.

8.3 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. Sample size re-estimation at the interim analysis will be based on Fisher's criterion (Fisher's combination test). For further details please refer to Section 13.5 Interim Analysis.

8.4 Pooling Strategy for Study Sites

Data will be pooled across all study sites unless indicated otherwise. Protocol deviations will be presented in total across all study sites and split by study sites.

8.5 Blood Sampling Schedule and Additional Blood Draws

The compliance of the study sites with the specified blood sampling schedule will be analyzed using frequencies and percentages. The number of subjects with blood draws inside and outside the defined blood sampling time window will be summarized per blood sampling time point and study site.

Laboratory measurements resulting from additional blood draws will not be presented in descriptive summaries, though will be listed and used in mixed-effects model repeated measures (MMRM) analysis.

8.6 Other Issues

Not applicable.

9. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

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

Other baseline/screening data include:

1. Indication for CRRT (cause of AKI will be specified)
2. Known allergies
3. Current medications and medications prescribed during the 30-day period prior to informed consent
4. Medical history
5. Physical examination

6. Vital signs
7. Laboratory parameters

The following describes the summary of the various types of baseline data either as continuous data or as frequency tabulation:

1. Age will be summarized as a continuous variable across subjects, and as frequencies within age groups (18-35, 36-45, 46-55, 56-65, >65 years).
2. Height, weight, BMI and illness severity score APACHE II will be summarized as a continuous variable across subjects.
3. The frequencies for gender, ethnicity and race will be tabulated.
4. The frequencies for current medications and medications prescribed during the 30-day period prior to informed consent will be tabulated based on the medication names coded according to the WHO Drug Dictionary.
5. Physical examinations will be tabulated as those findings which are deemed: 'Normal', 'Abnormal, Not Clinically Significant', 'Abnormal, and Clinically Significant'.
6. Vital signs will be summarized as a continuous variable across subjects.
7. Laboratory parameters will be summarized as a continuous variable across subjects. Laboratory results will also be listed with clinical significance.

Continuous data will typically be summarized using the number of subjects n, mean, standard deviation, minimum, median and maximum. Treatment comparisons will be based on t-test or Wilcoxon rank sum test, as applicable. Frequencies will be compared between treatment groups utilizing Fisher's exact test.

The following describes the baseline data that will only be listed:

1. Indication for CRRT (including specification for AKI subjects)
2. Known allergies
3. Medical history including Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, MedDRA Preferred Term, medical condition/surgical procedure reported term, date of onset and information if the medical history is still present and if it was treated.

10. ANALYSIS OF PHARMACOKINETICS AND PHARMACODYNAMICS

Not applicable.

11. TREATMENT COMPLIANCE AND EXPOSURE

Due to the ICU setting of the study, patient treatment compliance is not applicable.

Treatment exposure will be analyzed based on the percentage of the prescribed dose actually administered to the patient. Please refer to Section 13.3 Secondary Analysis for further details. Additionally, the number and percentage of subjects completing a certain overall CRRT treatment duration and the number and percentage of subjects using a certain number of extracorporeal circuits during the 120 hours evaluation period will be provided.

The number and percentage of subjects completing a certain extracorporeal circuit treatment time of the defined maximum 72 hours period for which each Prismaflex M150 Set can be used continuously along with reasons for treatment termination and location of clotting (Prismaflex M150 set or blood access device or in both) will be provided as well.

Overall CRRT treatment duration and the number of extracorporeal circuits used during the 120 hours evaluation period will be summarized using the number of subjects n, mean, standard deviation, median, minimum and maximum.

12. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

No changes in conduct or planned analyses from the protocol.

13. EFFICACY PARAMETERS

13.1 Primary Analysis

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

The extracorporeal circuit life of a filter that is replaced due to continuous use for 72 hours, will be censored for the statistical analysis. 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 and switches to therapies other than Prismocitrate 18 or control), 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 system alarms/conditions and confirmed by an Independent Adjudicator will be considered ‘events’ in the statistical survival analysis.

The context and data/time of two alarms (as below) used in the independent adjudication

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

will be derived from the data card. The date and time of first occurrence of one or both alarms above that could not be successfully mitigated by the study site, will be considered as the end of the filter life if the event (alarm) is confirmed to be caused by filter clotting by the independent adjudicator. Also, the date and time recorded on data card for filter start, replace and/or end will be used to calculate the filter life during the independent adjudication.

If the reason for a filter change recorded on the eCRF is different from the indication from adjudication result (e.g. eCRF recorded a reason for filter change for any reasons other than the two alarm, but the adjudication result showed as filter clotted), the adjudication result will be used to determine if it is considered an 'event' in the statistical survival analysis.

In some scenarios, where no independent adjudication could be performed (e.g. missing data card file), the eCRF recorded filter start, end, and change reason will be used in the analysis of filter life.

Filters used after a patient crossed-over treatment to the other study treatment group (switch from Prismocitrate 18 to Control, or switch from Control to Prismocitrate 18) will be analyzed under the original, randomized treatment assignment following the intent-to-treat principle. 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). The potential dependence between extracorporeal circuit lives within the same patient will be accounted for using a clustered log rank test.

Separate estimates per treatment group will be provided for the primary endpoint based on Kaplan-Meier methodology. These estimates of the survival functions will be graphically displayed and tabulated as cumulative distribution functions. Characteristic values of these functions such as Q1, median survival time and Q3, will be provided and differences between estimated survival functions will be assessed using a clustered log rank test [11].

This clustered log rank test provides advantages over readily available methods to analyze clustered survival data, such as the PHREG procedure using the covariance sandwich estimator option and the NLMIXED procedure for accelerated failure time frailty models, both available in SAS, due to its complete non-parametric nature. No

assumptions about the distribution of the data or the structure of the covariance matrix have to be made. Details on the underlying clustered log rank test are provided in Section 13.1.1 Hypothesis Regarding Primary Endpoint.

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

An interim analysis will be carried out after 50% of subjects completed treatment. Please refer to Section 13.5 Interim Analysis 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 (critical value based on Bauer & Koehne[9] 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 (c_α) which guarantees that the overall Type I error is controlled and preserved at a maximum of 0.05:

$$p_1 p_2 \leq c_\alpha = \exp[-\frac{1}{2}\chi_4^2(1-\alpha)]$$

where p_1 is the observed error probability for the test in the subsample of subjects investigated before the interim analysis,

and p_2 is the observed error probability for the test in the subsample of subjects enrolled after the interim analysis,

and $\chi_4^2(1-\alpha)$ is the (1-α)-quantile of the central χ^2 distribution with 4 degrees of freedom.

If $p_1 \leq c_\alpha$ one could already stop at the interim analysis with the rejection of the null hypothesis since $p_2 \leq 1$ holds per definition.

13.1.1 Hypothesis Regarding Primary Endpoint

The following hypothesis will be tested to compare the Prismaflex M150 Set extracorporeal circuit life between Prismocitrate 18 and Control group.

Null hypothesis	H_0: $\Lambda_P = \Lambda_C$
Alternative hypothesis	H_A: $\Lambda_P \neq \Lambda_C$

where Λ_P relates to the cumulative hazard function for the Prismocitrate 18 group and Λ_C relates to the cumulative hazard function for the Control group.

To test the null hypothesis, the following test statistic for the clustered log rank test will be calculated:

$$CLR = \sum_{g=1}^{2} \sum_{k=1}^{K_g} LR_{gk}$$

where g represents the treatment group (g = 1 for Prismocitrate 18 and g = 2 for Control) and LR_{gk} is a partition of the log rank statistic for group g and cluster k. The number of clusters K_g can differ between treatment groups g.

The total variance can be estimated from the within cluster mean squared error MSE_{gk}. Since the clusters and treatment groups are independent the MSE_{gk} can be summed across clusters to find the total variance for CLR:

$$\text{var}(CLR) = \sum_{g=1}^{2} \sum_{k=1}^{K_g} MSE_{gk}$$

$$MSE_{gk} = E(LR_{gk})^2$$

The log rank statistic for group g and cluster k can be derived as follows:

$$LR_{gk} = n \sum_{i=1}^{n_{gk}} \frac{\delta_{gki} W(t_{gki})}{Y_g(t_{gki})} - \sum_{g'=1}^{2} \sum_{k'=1}^{K_{g'}} \sum_{i'=1}^{n_{g'k'}} \frac{\delta_{g'k'i'} Y_{gk}(t_{g'k'i'}) W(t_{g'k'i'})}{Y_g(t_{g'k'i'}) Y(t_{g'k'i'})}$$

where W is a weight function specific to the log rank test:

$$W(t_{gki}) = \frac{Y_1(t_{gki}) Y_2(t_{gki})}{Y(t_{gki})}$$

and n is the total number of observations,

n_{gk} is the number of observations in cluster k within treatment group g,

δ_{gki} is the number of failures in group g and cluster k,

$Y_g(t_{gki})$ is the number at risk in group g at the observed time (either censoring or failure) for observation i in group g and cluster k,

$Y_{gk}(t_{g'k'i'})$ is the number at risk in group g and cluster k at some time t where g', k' and i' can vary independent of g, k and i to any value within the range of g, k and i.

It has been proven that CLR converges to a normal distribution under H_0. Thus, the Wald test resolves to a standard normal distribution:

$$Z = \frac{CLR}{\sqrt{\text{var}(CLR)}} \sim N(0,1)$$

According to the standard procedure for any statistical test we will reject H_0 when Z exceeds the critical value for a given level of Type I error.

At Interim Analysis:

The p-value p_1 will be based on the test statistic Z above and on the subset of subjects completing treatment at the time point of the interim analysis (50% of subjects).

If $p_1 < 0.0087$, reject H_0 and claim difference in cumulative hazard function between treatment groups

If $p_1 \geq 0.0087$, do not reject H_0 and continue enrollment of subjects

At Final Analysis (End of Study):

The p-value p_2 will be based on the test statistic Z above and on the subset of subjects enrolled after the interim analysis (50% of subjects).

If $p_1 p_2 < 0.0087$, reject H_0 and claim difference in cumulative hazard function between treatment groups

If $p_1 p_2 \geq 0.0087$, do not reject H_0

13.2 Sensitivity Analysis

In order to check the robustness and validity of the primary analysis the analysis described under Section 13.1 Primary Analysis will be repeated using the PP. For this analysis filters used after a patient crossed over treatment to the other study treatment group will not be included.

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. The analysis of the primary efficacy endpoint will be repeated for 4 scenarios using the following assumptions for **cases where therapy (ie, a filter) was discontinued for reasons other than filter clotting**:

1. Assume for each of these cases in the Prismocitrate 18 group that filter clotting (the primary event of interest; please see Section 5.5.1 Primary Efficacy Endpoint) occurred at the time of therapy discontinuation for reasons other than filter clotting; Assume for each of these cases in the Control group that filter clotting occurred at the time of therapy discontinuation for reasons other than filter clotting.
2. Assume for each of these cases in the Prismocitrate 18 group that filter clotting occurred at the time of therapy discontinuation for reasons other than filter clotting; Assume for each of these cases in the Control group that filter clotting occurred at the largest event time observed in the Control group.
3. Assume for each of these cases in the Prismocitrate 18 group that filter clotting occurred at the largest event time observed in the Prismocitrate 18 group; Assume for each of these cases in the Control group that filter clotting occurred at the time of therapy discontinuation for reasons other than filter clotting.
4. Assume for each of these cases in the Prismocitrate 18 group that filter clotting occurred at the largest event time observed in the Prismocitrate 18 group; Assume for each of these cases in the Control group that filter clotting occurred at the largest event time observed in the Control group.

13.3 Secondary Analysis

A descriptive summary of systemic and post-filter blood iCa^{2+} concentrations as assessed at baseline (systemic only), 1 hour and every 6 hours during the 120 hours evaluation period and at 120 hours or end of the Evaluation period will be provided by treatment group. This summary will use the number of subjects n, mean, standard deviation, minimum, median and maximum. Changes from baseline will be analyzed by the number of subjects n, mean and standard deviation and t-test or Wilcoxon rank sum test, as applicable.

The individual blood iCa^{2+} concentrations will further be displayed graphically over time for each of the two treatment groups.

A MMRM analysis will be deployed to evaluate differences between treatment groups in blood iCa^{2+} concentrations that are collected at baseline, 1 hour and every 6 hours during the 120 hours Evaluation period and at 120 hours or end of the Evaluation period from the initiation of CRRT. The model will include the illness severity score APACHE II, baseline iCa^{2+} concentration, treatment group and time point as fixed effects, and an interaction between time point and treatment group will be included in the model only if treatment effects differ statistically significantly over time ($p < 0.01$).

In addition, frequencies and percentages will be provided for $iCa^{2+} < 1.1$ mmol/L by time point and treatment group (threshold indicative of decrease in iCa^{2+} despite adequate calcium compensation).

Daily delivered dose and overall delivered dose (both in mL/kg/hour) will be summarized using the number of subjects n, mean, standard deviation, minimum, median and maximum, as applicable. Treatment exposure will be analyzed carrying out the same descriptive summary for the percentages of the prescribed dose actually administered to the patient.

Effluent rate is considered an appropriate surrogate for the CRRT dose. Therefore, prescribed and delivered CRRT dose will be derived as follows based on the University of Alabama at Birmingham Continuous Venovenous Hemodiafiltration Protocol[12] used in the study:

$$Q_E = Q_{PBP} + Q_D + Q_{FR} + Q_R$$

where Q_E is the effluent rate (mL/hour),

Q_{PBP} is the pre-blood pump infusion rate which is the Prismocitrate 18 flow rate (mL/hour),

Q_D is the dialysate flow rate (mL/hour),

Q_{FR} is the patient fluid removal rate (mL/hour), and

Q_R is the post-filter replacement fluid rate (mL/hour).

If one of the rate is missing, effluent rate will not be able to calculate.

The prescribed dose (effluent rate) is calculated as:

$$Prescribed\ Effluent\ Rate = Body\ Weight \times 25\ mL/kg/hr$$

If there are multiple records of effluent rate per day (e.g. due to infusion rate change) the average value will be used to calculate the delivered dose for that day.

The percentage of the prescribed dose actually administered to the patient will be calculated by dividing the actual effluent rate by the prescribed effluent rate. 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 I error is controlled and preserved at a maximum of 5%.

The analysis of secondary efficacy endpoints will be carried out on the FA based on the randomized treatment groups (intent-to-treat principle).

[redacted]

[redacted]

13.4 Exploratory Analyses

Not applicable.

13.5 Interim Analysis

The analysis described under 13.1 Primary Analysis will be carried out after 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 & Koehne procedure with no early stopping for futility) on the FA, 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 (please see Section 13.1 Primary Analysis for details). This approach guarantees that an overall Type I error of 0.05 is preserved.

In order to re-assess the sample size for the subset of subjects recruited after the interim analysis, simulation studies will be run utilizing the p-value observed at the interim analysis (p_1). The re-assessment of the sample size will be carried out using the original assumptions for median circuit life times in the two treatment groups ([redacted] in the Prismocitrate 18 and control group) and will target a conditional power of 90% for rejecting the null hypothesis given the observed results of the interim analysis.

13.6 Subgroup Analyses

No specific subgroup analyses are planned.

14. SAFETY AND TOLERABILITY

Parameters to be tabulated for safety include the following: AEs/SAEs; bleeding events and transfusions; serum bicarbonate, pH and base excess, blood total calcium, blood total calcium/iCa^{2+} ratio, and serum electrolytes; anion gap; vital signs, creatinine, blood urea nitrogen, and bleeding parameters.

Any statistical analysis of safety endpoints will be carried out on the FA based on the actual treatment groups.

14.1 Adverse Events (AEs)

The outcome/resolution of all AEs and SAEs will be determined by the Investigator and documented on the AE case report form (CRF)/SAE report form.

An overview of the number of subjects with at least one AE, at least one SAE, at least one study product-related AE, at least one study product-related SAE, and withdrawn due to SAE will be summarized (frequency and percentage of subjects).

An overview of the number of AEs, SAEs, study product-related AEs, and study product-related SAEs along with rates of events per subject treatment days will be tabulated.

The number of subjects with at least one AE (Serious and Non-Serious) will be summarized by MedDRA System Organ Class and MedDRA Preferred Term (frequency and percentage of subjects). The number of AEs (Serious and Non-Serious) and the rates of AEs per subject treatment days will be summarized by MedDRA System Organ Class and MedDRA Preferred Term. In addition, the number of subjects with at least one AE (Serious and Non-Serious) will be summarized by MedDRA System Organ Class, MedDRA Preferred Term and Severity (mild, moderate, severe) (frequency and percentage of subjects).

The number of subjects with at least one study-product related AE (Serious and Non-Serious) will be summarized by MedDRA System Organ Class and MedDRA Preferred Term (frequency and percentage of subjects). The number of study-product related AEs (Serious and Non-Serious) and the rates of study-product related AEs per subject treatment days will be summarized by MedDRA System Organ Class and MedDRA Preferred Term. In addition, the number of subjects with at least one study-product related AE (Serious and Non-Serious) will be summarized by MedDRA System Organ Class, MedDRA Preferred Term and Severity (mild, moderate, severe) (frequency and percentage of subjects).

Any subject-based analysis of AEs (e.g., number of subjects with at least one AE) will be based on the worst severity reported for the subject for the event analyzed. If, for example, a subject reports two mild and one moderate AE(s), in the subject-based analysis the event will be presented only once under moderate severity. Study product-related AEs will be considered those AEs classified as probably or possibly associated with the device or drug. AEs unrelated to study product will be considered those with a causality assessment of unlikely or not associated. If the relationship to the drug/device is not available or not assessable, the respective AE will be classified as study product-related.

Data listings for AEs and SAEs will contain MedDRA System Organ Class, MedDRA Preferred Term, diagnosis, start date, stop date, severity, action taken regarding study product, relationship to study product and outcome.

Adverse events reported between signing the ICF and first study treatment will be listed separately.

14.2 Bleeding Events and Transfusions

The location of bleeding events and the type of transfusions will be summarized using frequencies and percentages. The number of subjects with bleeding events, the number of bleeding events, the duration of bleeding events, the number of subjects requiring transfusions and the number of transfusions will be summarized presenting frequencies and percentages for categorized data observed, and summarizing the original data using the number of values n, mean, standard deviation, median, minimum and maximum. The estimated blood loss and the units transfused will be summarized using the same statistics. Bleeding events and transfusions resulting from complications related to blood loss will be listed by patient.

14.3 Serum Bicarbonate, pH, Blood Total Calcium and Serum Electrolytes

Serum bicarbonate, pH (ABG), blood total calcium concentrations and serum electrolytes (sodium, potassium, chloride, phosphate, magnesium) will be analyzed in the exact same manner as blood iCa^{2+} concentrations.

Along the lines of Section 13.3 Secondary Analysis descriptive summaries will be carried out for each parameter at the different assessment time points, and changes from baseline will be analyzed. A MMRM analysis will be deployed for the different parameters following the description under Section 13.3.

The total calcium/iCa^{2+} ratio will only be summarized descriptively. Frequencies and percentages will be provided for pH < 7.2 by time point and treatment group (threshold indicative of metabolic acidosis). Frequencies and percentages will further be provided for total calcium/iCa ratio > 2.1 by time point and treatment group (threshold suggestive of citrate accumulation) as well as for anion gap > 11 mmol/L (threshold indicative of metabolic disturbance) and base excess < -5 mmol/L.

Complete blood count and blood lactate measurements obtained at screening will be listed by patient.

14.4 Vital Signs, Creatinine, Blood Urea Nitrogen and Bleeding Parameters

Descriptive summaries of vital signs (systolic and diastolic blood pressure, mean arterial pressure, respiratory rate, pulse, body temperature, weight and height), creatinine, BUN and bleeding parameters (PT/INR, PTT, hemoglobin, hematocrit, platelet count) as assessed at the different measurement time points will be provided. These summaries will use the number of subjects n, mean, standard deviation, minimum, median and maximum. Changes from baseline will be analyzed by the number of subjects n, mean and standard deviation and t-test or Wilcoxon rank sum test, as applicable.

An analysis of covariance (ANCOVA) model will be deployed to evaluate differences between treatment groups in the final measurements available for the parameters listed above. The model will include the independent variable treatment group and the covariates illness severity score APACHE II and parameter baseline value and will evaluate mean differences in the final parameter measurements.

15. OTHER RELEVANT DATA ANALYSES/SUMMARIES

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 hours evaluation period. A descriptive summary of training results on administration of Prismocitrate 18 will be provided in the Clinical Study Report. This summary will cover Citrate Training/Assessment Questions, and CRRT Clinical Cases provided by Dr. [redacted], [redacted], in her role as [redacted] for this study.

Individual data collected on initial treatment prescriptions and changes during the evaluation period, on dialysate, replacement solution, priming solution, calcium gluconate or calcium chloride used during the evaluation period will be provided in data listings. Likewise, detailed CRRT treatment information, Prismaflex M150 Set information, blood access information and CRRT machine and treatment modality will be listed.

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19. DOCUMENT HISTORY

Version No.	Change(s) in the Document	Reason for Change(s)	Approval Date
1.0	N/A (Initial Release)	N/A	17 JUN 2015
2.0	1) Added last paragraph to Section 5.5.1 Primary Efficacy Endpoint; 2) Removed first paragraph from Section 13. Efficacy Parameters; 3) Added first two paragraphs to Section 13.1 Primary Analysis; 4) Added wording on statistical testing of potential differences in the percentage of overall prescribed dose actually administered at the end of Section 13.3 Secondary Analysis.	1) Further clarification of the nature of the primary efficacy endpoint and of the event definition based on FDA request; 2) Covered by the paragraph added. Initial paragraph no longer needed; 3) Provision of additional details on the primary analysis based on FDA request; 4) Pre-specify secondary endpoints that could lead to additional labeling claims and control the Type I error rate for testing such endpoints as recommended by the FDA	07 AUG 2015
3.0	1) Added description of determination of alarm cause by Independent Adjudicator to Section 5.5.1 Primary Efficacy Endpoint; 2) Added anion gap to Section 4.2 Secondary Objectives and Section 5.6 Safety Measures; 3) Updated exclusion criteria in Section 6. Study Populations; 4) Added wording on sensitivity analysis for potential impact of informative censoring at the end of Section 13.2 Sensitivity Analysis; 5) Added analysis for iCa relating to threshold indicative of decrease in iCa despite adequate calcium compensation to Section 13.3 Secondary Analysis; 6) Updated Section 13.5 Interim	1) Process improvement in assessment of primary efficacy endpoint upon FDA request; 2) Additional parameter included upon FDA request; 3) Clarified and detailed out exclusion criteria based on FDA request; 4) Additional assessment of the potential impact of informative censoring on the primary efficacy endpoint upon FDA request; 5) Additional analysis included based on FDA request; 6) Provision of specific process/rule	10 FEB 2016

	Analysis with a specific process/rule for re-assessment of the sample size; 7) Added analysis relating to potential citrate accumulation and metabolic issues to Section 14.3 Serum Bicarbonate, pH, Blood Total Calcium and Serum Electrolytes.	upon FDA request; 7) Additional analysis included based on FDA request.	
4.0	1.) Updated: Author to Mengqi Xiao and Responsible Medical Officer to Qing Li. 2.) Updated Study Design, applied new template and changed corresponding the section numbering. 3.) Updated Formulation/Indication 4.) Updated wording in: Background and Rational, Primary Objective, Primary Efficacy Endpoint 5.) Updated Schedule of Events 6.) Updated Section 6 (Inclusion criteria) 7.) Updated Section 9 (Demographics) 8.) Updated Tables for 5.4.1 and 5.4.2	1.) Reflect Study Team changes 2.) Updating wording to match that of protocol amendment 2 3.) Updating wording to match that of protocol amendment 2 4.) Updated wording to match that of protocol amendment 2 5.) Updated wording to match that of protocol amendment 2 6.) Updated wording to match that of protocol amendment 2 7.) Updated wording to match that of protocol amendment 2 8.) Updated the schedule of events and blood sampling tables to reflect those tables found within the protocol.	26 JUN 2018

Statistical Analysis Plan: 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
Study Design	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 US and Canada.
Product Name:	Prismocitrate 18
Formulation/Indication:	A replacement solution indicated for regional anticoagulation of the extracorporeal circuit in patients undergoing continuous renal replacement therapy (CRRT)
Statistician:	[redacted] [redacted] Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015 Tel: [redacted] Email: [redacted]
Sponsor:	Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015
Responsible Medical Officer:	[redacted] MD, PhD [redacted] Baxter Healthcare Corporation
Final Date:	2018 AUG 02
Version:	4.0 Amendment 1

[redacted]

1. SIGNATURE PAGE

Study Title:	Clinical Evaluation of Use of Prismocitrate 18 in Patients Undergoing Acute Continuous Renal Replacement Therapy (CRRT)
Study Number:	1407-004
Statistician:	[redacted]

I have read this statistical analysis plan and confirm that to the best of my knowledge it accurately describes the planned statistical analysis of the study.

Prepared by:_____ Date:_____

[redacted]
Baxter Research & Development
Baxter Healthcare Corporation

Approved by:_____ Date:_____

[redacted] MD, PhD
[redacted]
Baxter Research & Development
Baxter Healthcare Corporation

Approved by:_____ Date:_____

[redacted]
[redacted]
Baxter Research & Development
Baxter Healthcare Corporation

1. SIGNATURE PAGE

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

Study Number: 1407-004

Statistician: [redacted]

I have read this statistical analysis plan and confirm that to the best of my knowledge it accurately describes the planned statistical analysis of the study.

Prepared by: [redacted] Date: [redacted]

[redacted]
Baxter Research & Development
Baxter Healthcare Corporation

Approved by: [redacted] Date: [redacted]

[redacted]
Baxter Research & Development
Baxter Healthcare Corporation

Approved by: [redacted] Date: [redacted]

[redacted]
Baxter Research & Development
Baxter Healthcare Corporation

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