Amendment 6.1 06 DEC 2017

Title:	Clinical Evaluation of the Prismaflex® HF20 Set and Prismaflex® System 7.10 for Acute Continuous Renal Replacement Therapy (CRRT) in Children

Compliance with GCP:	To be reviewed by Food and Drug Administration (FDA) as an IDE Application and by Clinical Study Site's Institutional Review Boards (IRBs)
Study type:	The study is being conducted at the request of the FDA to Support a 510(k) Clearance for the Prismaflex HF 20 Set under an FDA approved IDE Application
Study Product:	Prismaflex® HF20 Set and Prismaflex® System Software Version 7.10 or Prismaflex HF20 Set and Prismaflex System Software Version 7.20
Control Product:	Not Applicable
Study Sponsor	Gambro Renal Products, Inc.
Number of treatments:	Minimum treatment period of 24 hours and Maximum treatment period of 72 hours per patient
Number of patients:	Maximum of 30 acute kidney injury patients
Target population:	Continuous Renal Replacement Therapy (CRRT)
Study duration:	Approximately one year

	Date
Original Protocol:	26 JUN 2012
Amendment 1:	17 JUL 2013
Amendment 2:	11 AUG 2014
Amendment 3:	24 OCT 2014
Amendment 4:	05 MAY 2015
Amendment 5:	15 JUN 2016
Amendment 5.1	13 JUL 2016
Amendment 6:	19 OCT 2017
Amendment 6.1:	06 DEC 2017

[redacted]

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LIST OF ABBREVIATIONS	
ACD	Acid-citrate-dextrose
ACT	Activated Clotting Time
AE	Adverse Event
AKI	Acute Kidney Injury
APTT	Activated Partial Thromboplastin Time
ARF	Acute Renal Failure
B2M	Beta -2 microglobulin
BP	Blood Pressure (mmHg)
BUN	Blood Urea Nitrogen
Ca/Ca^{++}	Calcium
CFR	Code of Federal Regulations
Cl	Chloride
CPD	Continuous Peritoneal Dialysis
Cr	Creatinine
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
CVVH	Continuous Veno-Venous Hemofiltration
CVVHD	Continuous Veno-Venous Hemodialysis
CVVHDF	Continuous Veno-Venous Hemodiafiltration
ECMO	Extracorporeal Membrane Oxygenation
ECV	Extracorporeal Circuit Volume
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FA	Full Analysis set
FDA	Food and Drug Administration
FUN	Fluid urea nitrogen
g/dl	grams per deciliter
GCP	Good Clinical Practices
GUI	Graphical User Interface
H	Hour
Hgb	Hemoglobin (g/dl)
ICU	Intensive Care Unit
ID	Identification (number for patient)

LIST OF ABBREVIATIONS	
IDE	Investigational Device Exemption
IFU	Instructions For Use
IRB	Institutional Review Board
K	Potassium
Kg	Kilogram
L	Liter
Lbs	Pounds
MAP	Mean Arterial Pressure (mmHg)
Min	Minute
Ml	Milliliter
mmHg	Millimeters of mercury
Na	Sodium
PO_4^{3-}	Phosphorous
PBP	Pre Blood Pump
PFR	Patient Fluid Removal
PI	Principal Investigator
PP	Per Protocol Analysis Set
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
SAE	Serious Adverse Event
SCr	Serum creatinine
SCUF	Slow Continuous Ultrafiltration
TMP	Transmembrane pressure (mmHg)
UADE	Unanticipated Adverse Device Effect
UF	Ultrafiltration
US	United States
510(k)	Section 510(k)[11] of the Federal Food, Drug, and Cosmetic Act
Note: For the purpose of this document, “Clinical Study Protocol” is similar to “Clinical Investigation Plan” or “Protocol”.	

SYNOPSIS	
Title	Clinical Evaluation of the Prismaflex® HF20 Set and Prismaflex® System 7.10 for Acute Continuous Renal Replacement Therapy (CRRT) in Children
Study type	This study will be performed under a FDA-approved Investigational Device Exemption Application (IDE).
Principal Investigator	[redacted], MD, [redacted]
Number of Investigational sites	6 (up to 15 sites)
Number of patients	Up to 30 pediatric acute kidney injury (AKI) patients
Target population	Pediatric AKI patients treated with CRRT
Study Product	Prismaflex HF20 Set and Prismaflex System Software Version 7.10 or Prismaflex HF20 Set and Prismaflex System Software Version 7.20
Control Product	N/A
Number of treatments	Variable
Treatment duration	Variable
Study duration (per subject)	Patients will be treated for a minimum period of 24 hours up to 72 hours with the Prismaflex HF20 Set
Planned first patient Enrolled	November 2015
Planned last patient Enrolled	December 2018
Study rationale	This study is required for the clearance of a 510(k) Notification by the FDA for the Prismaflex HF20 Set
Study design	Multicentric, open label, single group study
Objectives	
Primary objective	The primary objective of this study is to evaluate the efficacy of the Gambro Prismaflex HF20 Set based on testing the hypothesis that it delivers sufficient renal replacement therapy (>38% reduction of BUN from baseline at 24 hours) to effectively treat AKI in pediatric patients weighing ≥8 and <20 kg (ie, ≥17.6 and <44.09 lbs). This hypothesis will be tested as a percentage reduction from baseline and evaluated at 24 hours after CRRT initiation.

Secondary objectives	The secondary objectives of this study are: • To evaluate the efficacy of removing creatinine and normalizing bicarbonate tested in a similar fashion to BUN. • To evaluate the safety of the Prismaflex System Software Version 7.10 and 7.20 in pediatric AKI patients weighing ≥8 and <20 kg (ie, ≥17.6 and <44.09 lbs). • To determine how long a duration of time each Prismaflex HF20 Set can be used up to a maximum of 72 hours from the initiation of CRRT in each patient.
Assessment Parameters	
Parameters for primary objective	Monitoring and recording of the change from baseline in BUN measured at 24 hours following initiation of CRRT.
Parameters for secondary objectives	Monitoring and recording patient's change from baseline in serum creatinine and bicarbonate. Monitoring and recording of Prismaflex System Software version 7.10 and 7.20 alarms related to fluid balance and control for effluent, dialysate, replacement solutions, and Prismaflex syringe volumes. The Prismaflex HF 20 Set life will be assessed by the duration of time for which each Prismaflex HF20 Filter Set can be used up to a maximum 72 hour period in each patient. The end of the extracorporeal circuit life will be defined by the occurrence of one or both of the following Prismaflex System alarms, after which CRRT will be terminated and the extracorporeal circuit replaced: • "Warning: Filter Clotted", and/or • "Caution: TMP Excessive". Another secondary endpoint is to demonstrate the safety of the Prismaflex® System Software Version 7.10 and 7.20 in pediatric AKI patients weighing ≥8 and <20 kg (ie, ≥17.6 and <44.09 lbs) by monitoring and recording Prismaflex alarms related to fluid balance as well as AEs, SAEs and device deficiencies. Alarm events from Prismaflex System Software Version 7.10 and 7.20 related to fluid balance will be noted and recorded for: • "Flow Problem" Caution, • "Gain Limit Reached" Warning, • "Loss Limit Reached" Warning.
Main selection criteria	\

<table>
<tr><td>Inclusion criteria</td><td>
1. Patients with a hospital admission body weight ≥8 and <20 kg (ie, ≥17.6 and <44.09 lbs).
2. Patients with AKI defined as either 1) AKI by the Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Guideline serum creatinine criteria, which is a >50% rise in serum creatinine over baseline or a 0.3 mg/dL SCr rise in 48 hours OR 2) as AKI by the Pediatric modified Risk, Injury, Failure, Loss, End-Stage Renal Disease (pRIFLE) criteria which is a 25% reduction in estimated creatinine clearance,[16] OR 3) a serum creatinine >1.2 mg/dL. OR
Patients with severe fluid overload, defined as a >10% fluid accumulation, relative to the ICU admission.
3. Patients who have received renal replacement therapy previously can be included in the study if >24 hours have elapsed since previous RRT provision.
Provide written informed consent from one or both parents, as required by the local IRB or legal guardians, unless one parent is deceased, unknown, incompetent or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child per 21 CFR Part 50.55(e).
</td></tr>
<tr><td>Exclusion criteria</td><td>
1. The following hemoglobin exclusion criteria apply:
<table>
<tr><td>Weight</td><td>Starting Hgb (g/dl)</td><td>Exclusion Criteria</td></tr>
<tr><td>8.0-20.0 kg</td><td><7.0</td><td>Excluded</td></tr>
<tr><td>8.0-12.0 kg</td><td><8.0</td><td>Excluded unless blood prime is used</td></tr>
<tr><td>12.1-20.0 kg</td><td><7.5</td><td>Excluded unless blood prime is used</td></tr>
</table>
2. Children who are wards of the state.
</td></tr>
</table>

Safety (AE, SAE)	To ensure the safety monitoring of adverse events (AEs), Unanticipated Adverse Device Effect (UADEs) and serious adverse events (SAEs) will be reported via an emergency reporting process as described in the protocol. Also alarms and device deficiencies will be reported.
Statistical analysis	The planned statistical analysis is described in the Statistical Analysis Plan located in Appendix I of the study protocol.
Regulatory	The study was submitted as an Investigational Device Exemption Application ([redacted]) and was approved by the FDA on 20Nov2014. The protocol and associated documents will be submitted to the Institutional Review Boards (IRBs) at each study site.

[redacted]

1. INTRODUCTION

1.1 Background and Rationale

Renal Replacement Therapies (RRTs) for acute kidney injury (AKI) mainly focus on the adult patient population, however children with a vast array of different AKI diagnoses also need some form of RRT until renal recovery occurs or a suitable transplant becomes available.

For acute RRT, children either receive treatment through peritoneal dialysis or extracorporeal dialysis. While Continuous Peritoneal Dialysis (CPD) is most often prescribed for infants with AKI, CRRT has become more commonly used for all children in the United States (US) and has been used effectively in infants <10 kg.[1,2]

Many aspects of pediatric CRRT need consideration such as vascular access, patient age and weight, extracorporeal volume, blood flow rates, ultrafiltration (UF) control,[3] the size of the dialyzer, the biocompatibility of the dialyzer,[4] frequency of treatment,[5] duration of dialysis[6] and center experience.

This clinical evaluation will focus on using a new high-flux dialyzer, Prismaflex® HF20 Set (Gambro Industries, France) and related support in the Prismaflex® System Software Version 7.10 and 7.20 (Gambro Lundia AB, Sweden) for CRRT in children in centers with extensive experience in pediatric dialysis.[7,8] Software Version 7.10 and Version 7.20 of the Prismaflex software have been developed to safely treat children weighing down to 8 kg with respect to fluid balance.

This study is being performed at the request of the US Food and Drug Administration (FDA). In a teleconference with the FDA, Gambro was advised that a clinical study with the Prismaflex HF20 Set would be required for the clearance of a 510(k) Notification by the FDA. This study will be performed under a FDA-approved Investigational Device Exemption Application (IDE).

1.2 Benefits and risks for the study population

The patient will receive or continue to receive CRRT as part of study participation. Additional direct benefits to the patient from the use of the Prismaflex HF20 Set and Prismaflex Control Unit with software version 7.10 and version 7.20 are lower extracorporeal blood volume and refined fluid management capabilities that are more specific to patients with weights between 8 and 20 kg. As such, the patient's participation may help improve the delivery of CRRT to critically ill small children.

Foreseeable risks for the patients included in this clinical investigation do not differ from those usually observed during this type of treatment.

No additional risk directly related to the use of the product can be objectively foreseen.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to evaluate the efficacy of the Gambro Prismaflex HF20 Set based on testing the hypothesis that it delivers sufficient RRT (>38% reduction of BUN from baseline to 24 hours) to effectively treat AKI in pediatric patients weighing ≥8 and <20 kg (ie, ≥17.6 and <44.09 lbs). This hypothesis will be tested as a percentage reduction of blood urea nitrogen (BUN) from baseline until 24 hours after CRRT initiation.

2.2 Secondary objectives

The efficacy in removing creatinine and normalizing bicarbonate will be tested in a similar fashion to BUN, both as secondary objectives. Another secondary objective of this study is to evaluate the safety of the Prismaflex System Software Version 7.10 and 7.20 in pediatric AKI patients weighing ≥8 and <20 kg (ie, ≥17.6 and <44.09 lbs). The measurement of the duration of time for which each Prismaflex HF20 Set can be used will be evaluated out to a time period of 72 hours from the initiation of CRRT in each patient.

2.3 Primary endpoints

The primary endpoint is the change from baseline in BUN evaluated at 24 hours following initiation of CRRT with the Prismaflex HF20 Set.

2.4 Secondary endpoints

The secondary endpoints are:

- The change from baseline in creatinine and bicarbonate measured at 24 hours following initiation of CRRT.
- The Prismaflex HF20 Set extracorporeal circuit life assessed by the duration of time for which each Prismaflex HF20 Set can be used out to a maximum 72 hour period in each patient.
- To demonstrate the safety of the Prismaflex System Software Version 7.10 and 7.20 in pediatric AKI patients weighing ≥8 and <20 kg (ie, ≥17.6 and <44.09 lbs)

by monitoring and recording Prismaflex alarms related to fluid balance as well as AEs, SAEs and device deficiencies.

3. STUDY DESIGN

The clinical study design is a multicentric, open label, single group study in which patients meeting all the inclusion criteria and none of the exclusion criteria of this protocol, and deemed treatable by their physician with the Gambro Prismaflex HF20 Set and Prismaflex System Software Version 7.10 or 7.20, will be enrolled in the study. Patients included in the analysis will be treated for a minimum period of 20 of the first 24 hours and up to 72 hours with each Prismaflex HF20 Set with BUN, creatinine and bicarbonate being measured for statistical analysis at 12 hour intervals during CRRT treatment. Each patient will provide a sequence of BUN, creatinine, and bicarbonate values (measured from baseline onward at 12 hour intervals) and may be treated on each Prismaflex HF20 Set for up to 72 hours.

The duration of time for which each Prismaflex HF20 Set can be used will be evaluated out to a time period of 72 hours from the initiation of CRRT in each patient. The end of the extracorporeal circuit life will be defined by the occurrence and failure to mitigate one or both of the following Prismaflex System alarms, after which CRRT will be terminated and the extracorporeal circuit replaced:

- “Warning: Filter Clotted”, and/or
- "Caution: TMP Excessive".

At 72 hours from the initiation of HF20 study CRRT, if the subject has been on the current Prismaflex HF20 set for less than 72 hours, the subject is allowed to continue on their current filter set until end of filter life (Refer section 3.2). The site may follow applicable institutional practices if additional CRRT is required.

Alarms from Prismaflex System Software Version 7.10 and 7.20 related to fluid balance will be noted and recorded for the following alarms:

- “Caution: Flow Problem”,
- “Caution: Gain Limit Reached”,
- “Caution: Loss Limit Reached”.

The weight, state of uremia, cardiac status and general physical condition of the patient must be carefully evaluated and recorded by the prescribing physician as required and, at a minimum, each day during treatment.

3.1 Study duration

The study is planned to start in November 2015 (First Visit, First Patient) and to stop in December 2018 (Last Patient, Last Visit). It may be terminated earlier if sufficient patient numbers (24) reach the primary endpoint of 24 hours of CRRT or later if 24 patients have not achieved the endpoint for analysis.

3.2 Study discontinuation rules

The Patient is allowed one interruption for a maximum period of less than or equal to 4 hours during the first 24 hours of CRRT. A filter set change is considered an interruption. A recirculation is also considered an interruption.

The HF20 Set can be changed only once during the first 24 hours. If the patient's study treatment is interrupted for ≥4 hours within the first 24 hours from CRRT initiation, the patient will be withdrawn from the study.

If the patient's study treatment is interrupted after the first 24 hours from CRRT initiation, the patient will have completed the study observation period. The patient cannot restart a new HF20 Set., and instead will return to standard of care.

If CRRT is no longer required and thus ends prior to 24 hours, then the patient is withdrawn from the study. In this case, no additional laboratory sampling is needed to support this study.

For patients who continue HF20 Set CRRT past 24 hours but CRRT ends between the 12 hour intervals, the last completed l2 hour interval value will be the last set of lab values included for analysis. No additional sampling is needed.

A subject will be discontinued from the study if he/she develops any condition for which the investigator believes, according to his/her medical judgment, the patient should discontinue from the study. The investigator will try to collect the end of study data if possible.

3.3 Study product and material

The Prismaflex HF20 Set is indicated for use only with the Prismaflex System equipped with software Version 7.10 and Prismaflex System Software Version 7.20 in providing

continuous fluid management and RRT. The system is intended for patients who have AKI, fluid overload or both, taking into consideration the patient's access, blood flow, body weight and the extracorporeal blood volume. The Prismaflex HF20 Set is intended for use in the following veno-venous therapies: CVVH, CVVHD and CVVHDF. The Prismaflex HF20 Set should be restricted to patients with a body weight ≥8 kg (17.6 lb.) and <20 kg (44.09 lb).

The Prismaflex HF20 Set incorporates a membrane which is identical to the membrane used in the Gambro HF1000 and HF1400 sets, both of which have been previously cleared by the FDA for marketing and clinical use in the United States (K042938). The Prismaflex HF20 Set dialyzer contains the Polyamix™ membrane, which is hemocompatible and able to effectively reject dialysate contaminants. More specifically, the membrane contains 0.22 m^2 of polyarylethersulfone/polyvinyl-pyrrolidone membrane, which is almost identical in composition to the membrane used in other Gambro Polyflux hemodialyzers (ie, Polyflux 6H, 140H, 170H, 210H) which have been previously cleared by the FDA for marketing and clinical use in the US. Therefore, low treatment-induced inflammation is to be expected from the use of the Prismaflex HF20 Set which utilizes a similar membrane as that studied by Schindler et. al.[9] The membrane in the Prismaflex HF20 Set has an inner diameter of 215 µm and a wall thickness of 50 µm and is sterilized by steam, which is the same sterilization method used for the previously cleared Gambro Polyflux hemodialyzers. The blood priming volume of the extracorporeal circuit for the HF20 set is 60 mL and is lower than previously cleared Gambro Polyflux hemodialyzers and CRRT circuits due to its pediatric application.

Gambro will provide each investigational site with one Prismaflex System equipped with software version 7.10 or Prismaflex System Software Version 7.20. The provided machine may only be used on patients participating in the clinical study according to the FDA IDE regulations.

The FDA has not given 510(k) clearance for use of either the Prismaflex HF20 Set or the Prismaflex System Software Version 7.10 and Prismaflex System Software Version 7.20 for use in patients weighing <20 kg (44.09 lbs).

Please refer to the Investigator Brochure in Appendix IV, for a more detailed description of the Prismaflex HF20 set and the Prismaflex System version 7.10 and Prismaflex System Software Version 7.20.

3.3.1 Study Product Labeling

Each Gambro Prismaflex HF20 Set and Prismaflex System having Software Version 7.10 or 7.20 will be labeled **"***CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."* per 21 CFR Part 812.5.

3.4 Product accountability

The investigators at each site will be supplied with the investigational products (Prismaflex System Software Version 7.10 or Prismaflex System Software version 7.20 and Prismaflex HF20 Sets) to be used during this clinical study. The accountability document must be filled in by the person in charge of receiving the products at site.

The Prismaflex HF20 Set must be stored in a safe place with restricted access. The Prismaflex HF20 Set and Prismaflex System Software Version 7.10 and 7.20 labeled for investigational use according to the FDA IDE regulations must only be used to treat patients enrolled in the study under the sole supervision of the investigator.

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

- Date and number of Prismaflex HF20 Sets received by the investigator at the study site
- Dated assignment of Prismaflex HF20 Sets dispensed by the investigator
- Number and code of faulty or destroyed Prismaflex HF20 Sets

At each visit, the Study Monitor must ensure that the investigator has sufficient number of Prismaflex HF20 Sets at his/her disposition and that the Prismaflex HF20 Sets are being used according to their specifications.

4. SELECTION AND WITHDRAWALS OF PATIENTS

4.1 Study population

The study will include up to 30 pediatric AKI patients with a body weight ≥8 and <20 kg (ie, ≥17.6 and <44.09 lbs). These patients must meet all inclusion criteria and none of the exclusion criteria defined for this study. Patients will be recruited from a select group of pediatric institutions, comprised of investigators from the Prospective Pediatric CRRT (ppCRRT) Registry Group – a multi-center collaborative that has published the vast majority of pediatric CRRT literature since 2004.[2,10-15]

4.2 Inclusion criteria

A subject must meet ALL of the following inclusion criteria in order to participate in this study:

1. Patients with a hospital admission body weight ≥8 and <20 kg (ie, ≥17.6 and <44.09 lbs).
2. Patients with AKI defined as either 1) AKI by the Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Guideline serum creatinine criteria, which is a ≥50% rise in serum creatinine over baseline or a 0.3 mg/dL SCr rise in 48 hours OR 2) as AKI by the Pediatric modified Risk, Injury, Failure, Loss, End-Stage Renal Disease (pRIFLE) criteria which is a 25% reduction in estimated creatinine clearance,[16] OR 3) a serum creatinine ≥1.2 mg/dL.
   OR
   Patients with severe fluid overload, defined as a >10% fluid accumulation relative to the ICU admission.
3. Patients who have received RRT previously can be included in the study if >24 hours have elapsed since their previous RRT treatment.
4. Provide written informed consent from one or both parents, as required by the local IRB or legal guardians, unless one parent is deceased, unknown, incompetent or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child per 21 CFR Part 50.55(e).

4.3 Exclusion criteria

Exclusion criteria are the following:

1. The following hemoglobin exclusion criteria apply:

Weight	Starting Hgb (g/dl)	Exclusion Criteria
8.0-20.0 kg	<7.0	Excluded

8.0-12.0 kg	<8.0	Excluded unless blood prime is used
12.1-20.0 kg	<7.5	Excluded unless blood prime is used

2. Children who are wards of the state.

4.4 Recruitment

Recruitment for the study will start after FDA approval of the Investigational Device Exemption Application (IDE) and the Institutional Review Board (IRB) approvals at respective study sites.

The parent(s) or legal guardian(s) of the patients who meet the inclusion and exclusion 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. One or both parents (as appropriate and as required by local IRB) must give their permission unless one parent is deceased, unknown, incompetent or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child per 21 CFR Part 50.55(e). The parent's or legal guardian's consent must be documented via signature and date on the Patient Informed Consent form. Patients will be considered enrolled in the study after the informed consent has been signed and a copy provided to the parents/guardian.

4.5 Patient withdrawal

The parent(s) or legal guardian(s) of the patients are free to withdraw their child from the study at any time without having to justify their decision. When a patient is withdrawn from a study, the parent(s) or legal guardian(s) will be contacted and given the opportunity to provide information about the reason(s) of withdrawal and possible occurrence of an AE.

Patients will be withdrawn from the study at any time for the following reasons:

- Patient no longer requires CRRT and ends therapy prior to receiving at least 20 hours of CRRT treatment,
- Patient requires a non-HF20 filter,
- Interruption of more than 4 hours from CRRT therapy (>4 hr interruption),
- More than one interruption of CRRT on the HF20 set regardless of duration, or

- Investigator Discretion

Reason for withdrawal will be recorded in the electronic Case Report Form (eCRF).

If withdrawal is related to the possible occurrence of AEs, the patient will be followed up according to the AE procedure.

4.6 Analysis Population Definitions

Full Analysis Set (FA): The Full Analysis Set is based on the intent-to-treat principle and includes any patient who received CRRT on the Prismaflex HF 20 Set for any period of time.

Per-Protocol Analysis Set (PP): The Per-Protocol Analysis Set defines a subset of the FA including patients who:

- fulfilled all inclusion criteria
- did not meet any of the exclusion criteria
- received at least 20 hours of CRRT treatment on the HF20 filter with no more than 1 interruption which may have included a filter change
- did not have major protocol deviations that might impact the assessment of the primary endpoint
- have available measurements for the primary endpoint (BUN) at baseline (within 1 hour prior, and 15 min after initiation of CRRT) and at 24 hours (±1 hour) from start of CRRT

5. PATIENT TREATMENT

5.1 Treatment details

All patients will be followed from the time of obtained informed consent through the time they end participation in the study. Patients will be treated for a minimum period of 20 hours of the first 24 hours. They can be treated up to 72 hours on the same Prismaflex HF20 Set. In case of interruption at less than 24 hours, a subject may receive a second HF20 set. BUN, creatinine and bicarbonate are to be measured for statistical analysis at initiation of CRRT and at 12 hour intervals during CRRT treatment. During study CRRT treatment, activated clotting time (ACT), partial thromboplastin time (PTT), and activated partial thromboplastin time (APTT) (applicable to heparin use only) will be

measured as determined by the standard of care at each site. Patient ionized calcium and extracorporeal circuit (post circuit) ionized calcium will be measured per local standard of care (applicable to citrate use only). Each patient may be treated on the same Prismaflex HF 20 Set for up to 72 hours.

Treatments will be performed according to this clinical protocol and in accordance with the Instructions for Use (IFU) for the Gambro Prismaflex HF20 Set and the Operators Manual for the Prismaflex System Software Version 7.10 or 7.20. Treatments will be performed in accordance with the IFU and Operations Manual and managed in accordance with the local standard of care for pediatric CRRT.

5.2 Procedure to Minimize Fluid Balance Errors

All CRRT study clinicians will be trained on the use of Prismaflex System Software Version 7.10 and 7.20 and will have previously used Prismaflex in clinical practice. The training will also cover specific features in the Prismaflex System Software Version 7.10 and 7.20 that support safe and effective use of the Prismaflex HF20 Set, including:

- Prismaflex System Software Version 7.10 and 7.20 on-screen support for blood priming the Prismaflex HF20 Set
- Setting Prismaflex System Software Version 7.10 and 7.20 UF error limits during treatment setup
- Best practice during Prismaflex System Software Version 7.10 and 7.20 fluid bag changes and in handling of Prismaflex System Software Version 7.10 and 7.20 UF alarms

Monitoring for fluid balance errors will be based both on the UF alarms in Prismaflex System Software System Version 7.10 and 7.20 as well as through monitoring of the Prismaflex System Software Version 7.10 and 7.20. Measurement of fluid bag weights will employ an external scale. It is up to the discretion of the responsible physician investigator to decide how these will be measured. If performed, local clinical procedures are to be followed.

5.3 Prismaflex System Software Version 7.10 and 7.20 Alarm System for UF Errors

Prismaflex System Software Version 7.10 and 7.20 alarms will be issued based on immediate deviations between delivered and expected fluid weight on each bag of >20 g. A treatment shutdown will be issued and alarm given based on the cumulative UF error in a 3 hour sliding window.

The determination of an acceptable Prismaflex System Software Version 7.10 and 7.20 UF error limit follows from the UF rate error, which is not to exceed 0.1 mL/kg/min in order to avoid complications, up to and including hemodynamic instability. The UF error limit default is determined based on the cumulative UF rate error over a sliding 3 hours window. The Patient Fluid Removal accuracy (PFR acc) of the Prismaflex System Software Version 7.10 and 7.20 is considered in this interval (± 70 mL per 3 hours):

UF default error limit = 0.1 mL/kg/min × 180 min × BW – PFR acc

This default UF error limit is calculated based on the patient weight entered during the set-up phase of the treatment. As an example, a patient weight of 10 kg would result in a default error limit of:

UF default error limit = 0.1 mL/kg/min × 180 min × 10 kg – 70 mL = 110 mL

Determination of the actual limit may follow the calculated default value, but is ultimately up to the discretion of the prescribing physician investigator. In consideration of the patient's condition, a more stringent limit may apply.

The prescribed limit is settable down to a limit of 60 mL/3 hours and is entered by the device operator. This is a mandatory action in order to be able to proceed to patient connection. Once set, the UF error limit is active throughout the treatment.

Should the preset UF error limit be reached during treatment, the device monitoring system will issue an alarm and terminate the treatment. Treatment at this point cannot be re-started on the same filter. Occurrence of such events shall prompt a call to the investigator and should alert the personnel to reassess the patient before continuation of the treatment on a new disposable set.

5.4 Fluid Overload Calculations

Fluid overload will be calculated by the methods used by Goldstein and the Prospective Pediatric CRRT Registry Group: [Fluid in (L) – Fluid out (L)] /ICU admission weight (kg) * 100. The initial fluid overload will be calculated at the time of Study CRRT initiation and then at 12 hour intervals from that point until the end of the study. Blood pressure data, including mean arterial pressure, will be recorded either non-invasively or via an indwelling arterial catheter (present as part of clinical care and not for study purposes alone) at Study CRRT initiation and at 1 hour intervals from that point until end of study. If CRRT is discontinued before a 6 hours time point for hemodynamic reasons

or before a 12 hour time point for reasons related to fluid balance, the last measurements available prior to CRRT termination will be recorded as end of treatment.

5.5 Prismaflex Fluid Balance Data

There are two ways to track fluid balance data from the Prismaflex System. The first consists of recording data from the History Display section of Prismaflex and the second one is from the review of the log files on the Prismaflex technical data card.

5.5.1 Log Files on Technical Data Card

Prismaflex System Software Version 7.10 and 7.20 automatically saves a log file at the end of each CRRT treatment. These log files track all events and alarms occurring during Prismaflex CRRT to include pressures, scale weights, pump speed data, etc.

Logging data are saved on the Prismaflex technical data card after a completed treatment, during the unload sequence of the disposable set. The data contained in these files mirror the information that was displayed on the GUI of the Prismaflex during treatment, such as prescription data, treatment events (alarms, bag changes), as well as treatment data including UF volumes.

Data from the Prismaflex technical data card will be used for the following:

- to allow for the investigation of reported study related events
- as a source of data to allow for the analysis of technical parameters, including alarm rates, stability of software, etc.

5.6 Treatment: Prescriptive Guidelines

The treatment parameters (eg, flow rates, time, etc.), dialysates, replacement fluids and anticoagulants will be at the discretion of the physician investigator, but will be recorded on the eCRFs and must be consistent with the labeling as follows:

- Minimum combined convective/diffusive prescribed small solute clearance: 2000 mL/h./1.73m^2 patient BSA
- Maximum Blood Flow Rate: 100 mL/min
- Maximum TMP: 450 mmHg/kPa

5.6.1 Dialysates

Only prescribed commercially available sterile dialysate solutions with a density similar to saline solutions will be used with the Prismaflex System Software Version 7.10 and 7.20. Sterile dialysate solutions should be standardized and formulated in accordance to the patient's clinical needs. The use of nonsterile dialysates could induce risks of bacterial or pyrogenic contamination for the patient.

5.6.2 Replacement Fluids

Only prescribed commercially available replacement solutions with a density similar to saline solutions and which are labeled for intravenous injections will be used. Replacement Fluids should be standardized and formulated in accordance to the patient's clinical needs.

5.6.3 Anticoagulants

Anticoagulation plays an important part in extending filter life by retarding plugging and clotting. The type of anticoagulants used will be as prescribed by the physician. The IFU for the Prismaflex HF20 Set provides the following recommendations for heparinization below in Section 5.6.3.1 Anticoagulation Considerations.

5.6.3.1 Anticoagulation Considerations

According to the literature, continuous heparinization at a rate of 10 to 20 IU/kg/h ensures proper operation of the extracorporeal circuit when performing treatment with patients having normal coagulation status. Depending on the patient's condition, however, heparinization can be lowered to < 5 IU/kg/h. Heparinization can be controlled by partial thromboplastin time (PTT) measurements: in this case, PTT could be maintained at 20 to 30 seconds over baseline.[18] Many centers check Activated Clotting Times (ACTs) instead of PTT. Each center will follow its own clinical practice for circuit heparinization.

Many US centers, including those involved in this application, use regional citrate anticoagulation to prevent clotting of CRRT circuits. The ppCRRT Registry Group has shown that such practices lead to comparable filter lifespan with fewer side effects[1] and regional citrate anticoagulation has been suggested as the preferred method in the recent KDIGO AKI guidelines.[19] As general guidelines, some sites have altered their regional citrate protocol from this original published protocol, but all centers will perform their citrate protocol to achieve the following goals per their standard of care:

- Acid-citrate-dextrose [ACD (Baxter, McGaw Park)] will be the standard citrate solution and will be infused either via an external dedicated pump or the Prismaflex® Pre-Blood Pump (PBP) at a rate that is per local standard of care.
- A calcium containing solution will be infused at the patient's return access or via a separate central line in composition, concentration and at a rate that is per local standard of care.
- Initial citrate rates will be decreased by 50% of standard for patients with expected immature/decreased hepatic metabolic function (patients <1 year of age, or with acute/chronic hepatic failure).
- Paired (post filter) circuit and patient ionized calcium levels will be obtained per local standard of care.
- In addition, paired ionized calcium levels will be drawn one hour after any change in citrate or calcium infusion rates.
- The goals of regional citrate anticoagulation will be to achieve a circuit ionized Ca level of 0.25 to 0.45 mmol/L and a patient ionized Ca level of 1.0-1.5 mmol/L.
- Twice daily patient total calcium levels will be drawn to assess for total hypercalcemia or citrate accumulation.
- Patients with total calcium levels >12.5 mg/dl (hypercalcemia) but with desired ionized Ca levels will have the $CaCl_2$ rate decreased per local standard of care.
- Patients with total calcium levels >12.5 mg/dl AND low ionized Ca levels < 0.9 mmol/L will be diagnosed with citrate accumulation. The treatment for citrate accumulation will be managed by local standard of care but will include decreasing the citrate infusion rate or discontinuing it, increasing citrate clearance by increasing dialysis and/or replacement fluid rates, or both. Hourly paired ionized Ca levels will be obtained until the patient ionized calcium is > 1.0 mmol/L.

This protocol, or slight variations to it, has been reported in numerous pediatric publications.[2,20-22] Given the recent calcium chloride supply shortage in the US, a standard conversion will be used to substitute calcium gluconate to provide equimolar amounts of calcium to the patient. All of the study sites have over 6 years of experience with this citrate anticoagulation protocol.

5.6.4 Hypothermia prevention

When treating infants and children with the Prismaflex HF20 Set, the volume of the extracorporeal circuit and the high exchange volume/patient weight ratio may cause hypothermia. It is recommended to warm the blood with the Gambro Prismaflow Blood and Fluid Warmer or any other standard warming devices used in treatment of patients with a weight ≥8 kg and <20 kg.

5.6.5 Priming the Extracorporeal Circuit

Circuits will be primed per local standard of care. Since the extracorporeal volume (ECV) of the circuit is < 10% of the blood of patients in this study (weight 8-20 kg), priming with blood products will not be mandated, but the site may choose to do so based on their local standard of care and patient stability.

5.7 Contact and Delivery of Study Material:

Investigators that will be participating in this study will be sent a copy of this protocol along with any applicable regulatory documents. Once this protocol and regulatory documents have been received by a given study site, the study site will be contacted by sponsor's Clinical Study Monitor to encourage the site to complete and return the forms in an expeditious manner.

5.8 Data to be Collected

5.8.1 Patient Information to Be Collected Prior to Initiation of Treatment

The following data will be collected and recorded on the Case Report Forms for Screening.

1. Coded Patient I.D.
2. Inclusion/Exclusion Criteria
3. Signed Patient Informed Consent
4. Patient Demographics
   a. Gender
   b. Date of Birth
   c. Hospital Admission Weight, Height, and Body Surface Area
   d. Calculated Intravascular Blood Volume
5. Patient Medical Information
   a. Cause of Acute Kidney Injury

b. Diagnosis
c. Vital Signs
d. Medication History for the Last 7 Days
e. Medical and Surgical History

5.8.2 Treatment Data to Be Collected

The following data will be collected and recorded on the eCRFs and/or data card for each patient treatment using the Gambro Prismaflex HF20 Set and Prismaflex System Software Version 7.10 and 7.20.

5.8.2.1 Treatment Information

1. Date of Treatment
2. Sequential Number of Gambro Prismaflex® HF20 Sets used
3. Date and Time of Treatment Initiation and Discontinuation
4. Blood access information
5. Treatment Modality
   a. CVVHD (Hemodialysis)
   b. CVVHDF (Hemofiltration)
   c. CVVH (Hemofiltration)

5.8.2.2 Treatment Prescription

1. Patient Fluid Removal Flow Rate (ml/h)
2. Replacement Flow Rate (ml/h)
3. Blood Flow Rate (ml/min)
4. Dialysate Flow Rate (ml/h)
5. Pre-blood pump (PBP) Flow rate (ml/h)

5.8.2.3 Dialysate, Pre-blood Pump (PBP) and Replacement Solutions Used

1. Ionic Formulation
2. Brand Name
3. Volume used

5.8.2.4 Priming Solution(s) (volume and infusion rate)

1. Blood
2. Buffered Blood
3. Saline
4. Heparinized Saline
5. Albumin

5.8.2.5 Anticoagulation Information

1. Type of anticoagulant used
2. Administration method
3. Anticoagulant dose

5.8.2.6 Patient Clotting Parameters

1. ACT, PTT, APTT, or other according to Sampling Schedule in Section 5.9.

5.8.2.7 Treatment Blood & Dialysate Concentration Data

1. Blood Urea Nitrogen (BUN) – according to the Sampling Schedule in Section 5.9.
2. Fluid Urea Nitrogen (FUN) – according to the Sampling Schedule in Section 5.9.
3. Creatinine – according to the Sampling Schedule in Section 5.9.
4. Bicarbonate according to the Sampling Schedule in Section 5.9.
5. Serum sodium, potassium, chloride, calcium, phosphorous, beta 2 microglobulin (B2M) & albumin according to the Sampling Schedule in Section 5.9.
6. Dialysate fluid urea nitrogen (FUN) according to the Sampling Schedule in Section 5.9

5.8.2.8 Information on Interruptions/Filter Changes and Blood Loss

1. Reason(s) for filter change
2. Start time and Stop time of interruption.
3. Filter duration within treatment before clotting

4. Reason for interruption/Filter change
5. Complications related to filter clotting and associated AE (if applicable)
   a. Transfusion requirements
   b. Estimated blood loss

5.8.2.9 Total Fluid Removal, Fluid Overload, Blood & Mean Arterial Pressures

1. Amount (cumulative total) of fluid removed
2. End of study weight
3. Fluid overload at CRRT initiation and at 12 hour intervals up to end of study or 72 hours of CRRT according to the schedule in Table 2
4. Blood pressure including mean arterial pressure at admission to the ICU, at CRRT initiation and at hourly intervals up to end of study or 72 hours of CRRT according to the schedule in Table 2
5. Periodic Patient Fluid Removal (PFR) recorded from system GUI display hourly and before ending treatment
6. Unintended Patient Fluid Loss/Gain recorded from system GUI display at least every 1 hour and before ending treatment

5.8.2.10 Prismaflex Alarms Related to Fluid Balance

1. Alarm type (Caution: Flow Problem, Caution: Loss Limit Reached or Caution: Gain Limit Reached)
2. Operator Set Limit for Unintended Patient Fluid Loss/Gain *(mL/1h)*

5.8.2.11 Treatment and Outcome Data at end of study treatment

1. Total Prescribed Dose
2. Total Delivered Dose
3. Attainment of Dry weight (yes/no)
4. Attainment of Metabolic control (yes/no)
5. Continued need for RRT (yes/no)
6. Death (yes/no)
   a. Time of Death

b. Date of Death

c. Cause of Death

5.8.2.12 Adverse Events and Unanticipated Adverse Device Effect Information

1. Adverse Event

2. Start and Stop Date/Time

3. Causality

4. Seriousness

5. Action Taken

6. Outcome

5.8.2.13 Vital Signs

1. Height
2. Daily Weight
3. Pulse Rate
4. Respiratory Rate (Spontaneous or Mechanically Ventilated)
5. Temperature (location where temperature obtained)
6. Blood Pressure
7. Mean Arterial Pressure

5.8.2.14 Concomitant Medications

1. Medications up to 7 days prior to enrollment (medication name, minimum dose, maximum dose, frequency, route, start date and stop dates)
2. Medications taken during treatment, including any prescribed to treat an AE (medication name, minimum dose, maximum dose, frequency, route, start and stop dates).

5.9 Sampling Schedule

Patients will be treated for a minimum period of 24 hours with the measurement of BUN and creatinine at 12 hour intervals during dialysis treatment, see sampling schedule in Prismaflex HF20 Set & Prismaflex® System Software Version 7.10 and 7.20 Page 7 of 60

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Table 1. Blood Sampling Schedule

Solute	Prior to HF20 CRRT*	At Initiation of HF20 CRRT**	During HF20 CRRT	End of HF20 CRRT (if after 24 hour & between 12 hour interval)
Hemoglobin	Up to 24 hours prior to initiation of CRRT	As determined by local standard of care	As determined by local standard of care	N/A
BUN	Up to 24 hours prior to initiation of CRRT	Within 1hr prior to or within 15 minutes after CRRT initiation.	At +/- 1 hr of 12, 24, 36, 48, 60, & 72 hours	use previous 12 hour interval labs
FUN	NA	Within 1hr prior to or within 15 minutes after CRRT initiation.	At +/- 1 hr of 12, 24, 36, 48, 60, & 72 hours	use previous 12 hour interval labs
Creatinine	Up to 24 hours prior to initiation of CRRT	Within 1hr prior to or within 15 minutes after CRRT initiation.	At +/- 1 hr of 12, 24, 36, 48, 60, & 72 hours	use previous 12 hour interval labs
Bicarbonate	Up to 24 hours prior to initiation of CRRT	Within 1hr prior to or within 15 minutes after CRRT initiation.	At +/- 1 hr of 12, 24, 36, 48, 60, & 72 hours.	use previous 12 hour interval labs
Sodium	Up to 24 hours prior to initiation of CRRT	Within 1hr prior to or within 15 minutes after CRRT initiation.	At +/- 1 hr of 12, 24, 36, 48, 60, & 72 hours	use previous 12 hour interval labs
Potassium	Up to 24 hours prior to initiation of CRRT	Within 1hr prior to or within 15 minutes after CRRT initiation.	At +/- 1 hr of 12, 24, 36, 48, 60, & 72 hours	use previous 12 hour interval labs

Table 1. Blood Sampling Schedule

Solute	Prior to HF20 CRRT*	At Initiation of HF20 CRRT**	During HF20 CRRT	End of HF20 CRRT (if after 24 hour & between 12 hour interval)
Chloride	Up to 24 hours prior to initiation of CRRT	Within 1hr prior to or within 15 minutes after CRRT initiation.	At +/- 1 hr of 12, 24, 36, 48, 60, & 72 hours	use previous 12 hour interval labs
Phosphorous	Up to 24 hours prior to initiation of CRRT	Within 1hr prior to or within 15 minutes after CRRT initiation.	At +/- 1 hr of 12, 24, 36, 48, 60, & 72 hours	use previous 12 hour interval labs
Albumin	Up to 24 hours prior to initiation of CRRT	Within 1hr prior to or within 15 minutes after CRRT initiation.	At +/- 1 hr of 12, 24, 36, 48, 60, & 72 hours	use previous 12 hour interval labs
B2M	NA	Within 1hr prior to or within 15 minutes after CRRT initiation.	At +/- 1 hr of 24,48, & 72 hours	use previous 12 hour interval labs
ACT (Applies to heparin use only)	NA	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care
PTT (Applies to heparin use only)	NA	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care
APTT (Applies to heparin use only)	NA	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care
Total Ca	NA	As determined by local standard of care	As determined by local standard of care	NA
Extracorporeal Circuit ionized calcium (Not indicated when heparin or no anticoagulation are used)	NA	NA	As determined by local standard of care	NA
Patient Ionized Calcium (Not indicated when heparin or no anticoagulant are used)	NA	NA	As determined by local standard of care	NA

Table 1. Blood Sampling Schedule

Solute	Prior to HF20 CRRT*	At Initiation of HF20 CRRT**	During HF20 CRRT	End of HF20 CRRT (if after 24 hour & between 12 hour interval)

* Labs up to 24 hours prior to CRRT are required, unless the patient presents directly to ICU with immediate need for CRRT. Patient must meet all laboratory based inclusion criteria prior to starting treatment.

** "At initiation of CRRT" samples must be obtained within 1 hour prior to or within 15 minutes after treatment initiation. Labs drawn more than 1 hour prior to initiation will not be acceptable.

Table 2. Vital Signs & Fluid Overload Assessment Schedule				
Parameter	**12-24 Hours Prior to HF20 CRRT**	**At Initiation of HF20 CRRT – Baseline**	**During HF20 CRRT**	**End of HF20 CRRT (& if prior to 72 hours)**
BP (mmHg)	Within 24 hrs prior to CRRT	Within 1hr prior to or within 15 minutes after CRRT Initiation	Hourly (± 15 minutes)	At End
MAP (mmHg)	Within 24 hrs prior to CRRT	Within 1hr prior to or within 15 minutes after CRRT Initiation	Hourly (± 15 minutes)	At End
Degree of Fluid Overload*	Within 24 hrs prior to CRRT	Within 1hr prior to or within 15 minutes after CRRT Initiation	12, 24, 36, 48, 60, & 72 hours(± 1 hour)	At End

* Degree of Fluid Overload assessment = [fluid intake (L) – fluid output (L) / ICU admission wt (Kg)]×100%

** Re-assess and record baseline measurements if CRRT is being re-initiated (clot/interruption)

5.10 Emergency Procedure

The investigators are in charge of ensuring that the required procedures and skills are available in the event of any emergency situation during the study.

An SAE may constitute an emergency situation. As a consequence, any emergency situation developing during the clinical study period must be immediately reported to Gambro, whether directly related to the study or not.

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

In case of emergency, one of the following people shall be contacted in the shortest possible time and in the following order of priority:

[redacted]:
Document Owner

[redacted], M.D.
Tel:
Mobile:
e-mail:

[redacted]

[redacted] M.D.

[redacted]

[redacted]

Tel: [redacted]
Fax: [redacted]
Mobile: [redacted]

[redacted]

Tel: [redacted]
Email: [redacted]

6. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

An AE is any untoward medical occurrence in a patient or clinical investigational patient administered a study product and which does not necessarily have a causal relationship with the treatment or device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory function), symptom (rash, pain, discomfort, fever, dizziness, etc.), organ dysfunction (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 protocol 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 the end of the Prismaflex HF20 Set study treatment. During the course of the study, the Investigator or designee shall routinely monitor each patient for the occurrence of any AE. Routine monitoring should include regular communication with the trial patient, review of laboratory results and assessment of anticoagulation, dialysis access and medication use. 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 below when determining the relationship of the AE to the study product. The investigators may also discuss the event(s) with the sponsor 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 at defined visits 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/device 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 sponsor 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. Each investigator is to inform sponsor as soon as possible of all AEs or of any Unanticipated Adverse Device Effects (UADEs) associated with the Prismaflex HF20 Set and/or the Prismaflex Control Unit Software Version 7.10 and 7.20 that occurs during the course of the study/treatments, by telephone or email. Each investigator is to complete the electronic AE form in the EDC and, if applicable, the Serious Adverse Event (SAE) Report form and email it to the Prismaflex HF20 study email box. All SAEs and UADEs must be reported to the sponsor and the Data Safety Monitor. All UADEs must be reported to the reviewing IRB as soon as possible, but not later than ten working days after the investigator first learns of the effect per 21 CFR Part 812.150 (1).

Anticipated AEs and UADEs are defined as follows:

6.1 Anticipated Adverse events (AE)

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

- Air embolism
- Coagulation of the dialyzer/extracorporeal circuit resulting in blood loss
- Bradycardia
- Cramping
- Disequilibrium syndrome
- Dizziness
- Electrolyte Imbalance
- Excessive weight loss
- Fluid imbalance
- Hemodialyzer blood leak resulting in blood loss
- Hemolysis
- Hypersensitivity or Allergic Reactions “First Use Reaction”
- Hypertension
- Hypervolemia
- Hypotension
- Hypothermia
- Hypovolemia
- Infection
- Nausea
- Pyrogen Reaction
- Tachycardia
- Vomiting
- Bleeding

6.2 Unanticipated Adverse Device Effects

An UADE is defined as any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with, a device if that effect,

problem or death was not previously identified in nature, severity or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

All UADEs are to be recorded on the supplied SAE Initial Report and Follow-up Report forms, reported as an SAE and entered into an AE eCRF form in the EDC.

The sponsor must conduct an investigation of any unanticipated adverse device effect according to FDA regulations. If the sponsor determines that the unanticipated adverse device effect presents an unreasonable risk to subjects, the sponsor shall terminate all investigations or parts of investigations presenting that risk as soon as possible. This termination shall occur no later than 5 working days after the sponsor makes the determination and no later than 15 working days after the sponsor first received notice of the effect.

6.3 Other observation

Other observations which do not fall under the definition of AE or SAE concerning information related to any Gambro medical device that could indicate a safety risk for the patient need to be reported to sponsor. Examples could include deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a Gambro medical device, such as an error in labeling, packaging, device misuse or spontaneous report by a healthcare professional. For medical devices, this also includes technical issues such as unusual monitor alarms, damaged devices and/or handling problems.

6.4 Recording of AEs, SAEs and UADEs

All AEs and UADEs will be recorded on the AE eCRF form. For UADEs, additional information about the UADE will be recorded on the supplied SAE Report form. Initial reports and follow up reports will be indicated on the report forms. All AEs, SAEs and UADEs will be followed carefully until they resolve. Each AE, SAE or UADE will be described by:

1. Its duration
2. The severity grade
3. Its relationship to the study product
4. The action(s) taken.

Any patient death occurring during the study shall be considered as a SAE and the cause of death form shall be attached to the "SAE Form."

6.5 Evaluation of AEs, SAEs, and UADEs

6.5.1 Severity

The investigator will make an assessment of intensity for each AE, SAE and UADE reported during the study. The assessment will be based on the investigator's clinical judgment. The intensity of AE, SAE and UADE recorded in the eCRF should be assigned to the following categories:

- Mild: An event that results in transient discomfort, which is easily tolerated by the patient and does not interfere in a significant manner with the subject's normal functioning level with everyday activities. The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate: An event that produces limited impairment of function of normal everyday activities and can require therapeutic intervention, but produces no sequelae.
- Severe: An event that results in marked impairment of function and can lead to temporary inability to resume normal everyday activities. The AE produces sequelae requiring prolonged therapeutic intervention.

Comment: The term severity is often used to describe the intensity (severity) of a specific event. This is not the same as "seriousness," which is based on patient/event outcome or action criteria.

6.5.2 Causality

The relationship between the Prismaflex HF20 Set and/or the Prismaflex System Software Version 7.10 and 7.20 and the occurrence of each AE/SAE/UADE will be assessed and categorized as follows. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc., will be considered.

- Not related: Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event

- Unlikely related: An AE has little or no temporal relationship to the product and/or a more likely alternative etiology exists
- Related: An AE follows a strong temporal relationship to the product and another etiology is unlikely or significantly less likely
- Possibly related: An AE follows a reasonable temporal relationship to the product and an alternative etiology is equally or less likely compared to the potential relationship to the device or drug

Note: All AE/SAE/UADE judged by either the investigator or the Sponsor as having a reasonable "suspected" (ie, assessed at least as "Possible") causal relationship to an investigational study product qualify as an Adverse Reaction and may be subject to regulatory reporting timeline requirements.

6.5.3 Occurrence

- During treatment: An event arising during the procedure of treatment that includes the Prismaflex HF20 Set and/or the Prismaflex System Software Version 7.10 and 7.20.
- Between treatments: An event arising in between two procedures of treatment that includes the Prismaflex HF20 Set and/or the Prismaflex System Software Version 7.10 and 7.20.

6.5.4 Expectedness

Following definition should apply to define expectedness of an Adverse Reaction:

- Unexpected: Adverse reactions should be considered as unexpected if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information for the Prismaflex HF20 Set and/or the Prismaflex System Software Version 7.10 and 7.20.
- Expected: Adverse reactions should be considered as expected if the nature, seriousness, severity or outcome of the reaction(s) is consistent with the reference information for Prismaflex HF20 Set and/or the Prismaflex Control Unit. The expected/anticipated AEs are listed in Section 6.1.

6.5.5 Seriousness

An SAE is any untoward medical occurrence or affect that:

- Results in death; an event resulting in death
- Is immediately 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization: An event resulting in inpatient admission of the subject to the hospital. (Note: Inpatient hospitalization refers to any inpatient admission, regardless of the length of stay). Visits to the emergency room or outpatient facility do not constitute hospitalization for the purpose of this definition
- Results in persistent, permanent or significant disability or incapacity: An event that substantially interferes with the subject'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.
- Results in a congenital anomaly or birth defect: An abnormality detected at or after birth in the offspring of a study subject.
- Is medically significant as deemed by the investigator: A medically important event or reaction that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject 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.

Note:

- Medical judgment should be exercised in deciding whether an AE/reaction is serious in other situations. Important AEs/ reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject, or those that may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious,

- Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse effect.

7. ETHICS AND REGULATORY ISSUES

This study will be performed under a FDA-approved Investigational Device Exemption Application (IDE) and will be conducted in accordance with the IDE regulations (21 CFR Part 812).

7.1 Institutional Review Board (IRB)

The PI at each study site is responsible for Institutional Review Board (IRB) submissions. Sponsor will provide investigator with all needed documentation/data needed for IRB submission.

The Study Manager must receive a copy of the IRB approval letter and IRB approved Informed Consent Form, prior to the inclusion of patients in the study and before sending investigational products to the study site.

During the study, the investigator must report to the IRB any SAE and/or any amendment to the protocol, in accordance with local IRB requirements. All the correspondence with the IRB must be filed by the investigator.

7.2 Food and Drug Administration

The sponsor is in charge of submissions to the Food and Drug Administration (FDA).

The Study Manager must receive a copy of the IDE approval document supplied by the FDA, prior to the inclusion of patients in the study and before sending investigational products to the study sites.

7.3 Amendments

No amendment to study procedures shall be made without the mutual agreement of the investigators and sponsor. All such modifications must be duly documented and signed and are subject to protocol amendments. If any changes are made to the study design, the IRBs and FDA shall be informed and, when necessary, shall approve these changes prior to the enrollment of new patients except in emergency case for patient’s safety.

The sponsor Study Manager/Monitor is responsible for the distribution of an amendment to the FDA, investigators and other persons that are involved in the study. Investigators

are responsible for the distribution of this amendment to the members of their team and to their reviewing IRB.

7.4 Patient data protection

Each patient must be identified on the eCRF with an identification number indicating his/her rank of inclusion into the study. Investigators must keep the list of all the patients, including identification numbers, full names and last known addresses.

The parent(s) or legal guardian(s) of the patients must be informed in writing about the possibility of audits by authorized representatives of the company and/or regulatory authorities, in which case the relevant parts of study-related hospital records may be required.

The parent(s) or legal guardian(s) of the patients must also be informed that the results obtained will be computer-stored and analyzed, that local laws must be applied, that the child's confidentiality must be preserved, and that they are entitled to obtain any information concerning the data stored and analyzed by a computerized system.

7.5 Patient's information and informed consent

The parent(s) or legal guardian(s) of the 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. One or both parents (as required by local IRB and/or local laws) must give their permission unless one parent is deceased, unknown, incompetent, not reasonably available or when only one parent has legal responsibility for the care and custody of the child per 21 CFR Part 50.55(e). The parent's or legal guardian's consent must be documented via signature and date on the Patient Informed Consent form. The parent(s) or legal guardian(s) of the patients must also be informed that they are free to withdraw their child from the study at any time.

Patients will be considered enrolled in the study after the informed consent has been signed.

A sample Informed Consent Form can be found in Appendix II.

8. INVESTIGATIONAL PROCEDURES

8.1 Training

Sponsor, the PI and the Co-Investigators must make sure that any other staff participating actively in the study have been appropriately trained and received the relevant information relating to the performance of this study.

The Sponsor Study Monitor(s) will ensure that hospital staff involved in the study receives appropriate training for the purpose of the study.

If needed, a second training could be organized on study site request for clarification purposes.

8.2 Non-Compliance with the Protocol

In the event of any significant protocol deviation, the PI will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 5 working days after a deviation to eliminate an apparent immediate hazard to the subject. The PI will also notify the IRB of a protocol deviation made to eliminate an apparent immediate hazard to the subject.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the PI's participation. The sponsor will notify the IRB and applicable regulatory authorities of any investigator termination.

8.3 Monitoring (verification of compliance with protocol)

During the course of the study the sponsor monitor(s) will have regular contacts with the study sites and will make regular visits. Before the patient enrollment starts and during the course of the study, the sponsor monitor(s) will ensure that clinical facilities are acceptable, that the study site team complies with the protocol, the GCP, and that the study results are properly recorded on eCRFs.

It is important that investigator and/or another member of the team attend these visits. At monitoring visits, the sponsor monitor must ensure that the accountability of the investigational product is performed and that source data is checked. The study monitor must fill in a monitoring report for each study visit according to the monitoring procedure. The monitoring report will include notably information on the following:

- Patient's informed consent obtained prior to the start of the study
- Number of patients enrolled
- Performance of the treatments in accordance with the protocol
- Verification of source information to the data reported in the eCRF
- Compliance with inclusion and exclusion criteria according to the protocol.

8.4 Direct access to source documents

The investigator must give the Study Monitor direct access to relevant hospital or clinical records to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will leave the study site. Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of AEs and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

8.5 Source data verification

The investigators agree to allocate their time and the time of their staff to discuss findings and any relevant issues linked to source data.

8.6 Audits and inspections

The FDA may conduct an inspection during the study or after its completion.

9. STATISTICAL METHODS

The preliminary Statistical Plan for the study can be found in Appendix I. Further details of the planned statistical methods will be provided in the final statistical analysis plan. The purpose of the final statistical analysis plan is to elaborate on all statistical methods that will be used to evaluate the study primary and secondary endpoints, safety endpoints, and other relevant data (eg, demographics, baseline characteristics, treatment exposure and subject disposition) and describes analysis conventions to guide the statistical programming work. The statistical analysis plan will be finalized in accordance with sponsor's standard operating procedures.

10. DATA MANAGEMENT

10.1 Web-based Electronic Data Collection

Web-based electronic data entry must be completed for all patients enrolled in the study.

Electronic Investigator signatures will be used to attest to the accuracy of data entered into the electronic data collection system. Modifications made by the investigator or their delegated assistants will be tracked in the EDC system. Any data corrections as a result of data monitoring will be documented using an electronic generated query, as needed, and re-verified.

In collaboration with the investigators, the Study Monitor must ensure that data entered into the electronic data collection system are correct. Data editing for correction or

clarification purposes must be done before the case report forms have been transmitted for data processing and analysis. Subsequent corrections must be checked in writing and validated in signing by the investigators.

The eCRF data are the property of the sponsor. The investigators must ensure that the original source data are accessible to the Study Monitor, the Study Manager or any authorized people at any time during the course of the study.

10.2 Data entry and storage

The electronic data entry will be the responsibility of the investigator, along with the collection of Prismaflex data card.

The database and the data card will be maintained by sponsor. Data cards will be archived at the end of study.

10.3 Data management and quality control

Data management will be carried out by sponsor.

Sponsor is responsible of the creation of the study eCRF and the associated electronic database (EDC). Queries (ie, Data Clarification Forms) will be generated electronically in order to solve questions regarding missing data, unreadable text and coherence.

11. ADMINISTRATIVE PROCEDURES

11.1 Study documents and record keeping

Individual investigators are responsible for completing the eCRFs and the Study Monitor is responsible for reviewing them and clarifying and resolving any data queries. The completed and corrected electronic eCRFs for completed visits will be initially reviewed and approved by the Study Monitor initially and then sent for data processing. A copy of the eCRFs in PDF or electronic file will be provided by sponsor and is retained by the investigator, who must ensure that it is stored with other study documents such as the protocol, investigator’s brochure and any protocol amendments in a secure place with restricted access.

Data on subjects collected on eCRFs during the study will be documented in an anonymous fashion and the subject will only be identified by the subject number. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, the Study Monitor and the investigator are bound to keep this information confidential.

The investigator must maintain source documents for each subject in the study. All information on eCRFs must be traceable to these source documents, which are generally maintained in the subject's medical file. The source documents should contain all demographic and medical information, including laboratory data, as well as a copy of the signed informed consent, which should indicate the study number and title of the study.

11.2 Archiving of study documentation

The investigators must keep all original raw data together with the patient's identification list and signed informed consents for at least 30 years (the Sponsor reserves the right to require a longer archiving period related to the product lifespan).

Prior to destroying study-related documentation, the investigator shall contact the sponsor.

The investigator agrees to adhere to the document-retention procedures by signing the protocol.

12. SCHEDULE OF EVENTS

Assessment	**Up to 24 hrs prior to CRRT (Screening)**	**At initiation of CRRT (**Baseline)**	**12 hours**	**24 hours**	**36 hours**	**48 hours**	**60 hours**	**72 hours**	**HF20 CRRT End (if** between 12 hour visit intervals**)**
Inclusion	X								
Exclusion	X								
Informed Consent	X								
Demographics	X								
Vitals	X	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	X (± 15 min)
TMP		Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	X (± 15 min)
Record Periodic & Cumulative Patient Fluid Removal (from display)		Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	Hourly (± 15 min)	X (± 15 min)
Record Periodic Unintended Patient Fluid Loss/Gain		q 1 hr	q 1 hr	q 1 hr	q 1 hr	q 1 hr	q 1 hr	q 1 hr	X
Medical & Surgical History	X								
Diagnosis	X								

Assessment	**Up to 24 hrs prior to CRRT (Screening)**	**At initiation of CRRT (**Baseline)**	**12 hours**	**24 hours**	**36 hours**	**48 hours**	**60 hours**	**72 hours**	**HF20 CRRT End (if** between 12 hour visit intervals)
General Labs	Up to 24 hr prior	(Within 1 hr prior to or within 15 minutes after start of CRRT	+/- 1 hr	+/- 1 hr	+/- 1 hr	+/- 1 hr	+/-1 hr	+/-1 hr	If after 24 hours, may use previous 12 hour labs if CRRT ends between 12 hour assessment intervals hour time point acceptable
BUN	X	X	X	X	X	X	X	X	
Bicarbonate	X	X	X	X	X	X	X	X	
serum sodium	X	X	X	X	X	X	X	X	
Creatinine	X	X	X	X	X	X	X	X	
Potassium	X	X	X	X	X	X	X	X	
Chloride	X	X	X	X	X	X	X	X	
Phosphorous	X	X	X	X	X	X	X	X	
Albumin	X	X	X	X	X	X	X	X	
Total Calcium	X	X	*	*	*	*	*	*	*
Beta 2 Microglobulin		X		X		X		X	
Hemoglobin	X	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	NA

Assessment	**Up to 24 hrs prior to CRRT (Screening)**	**At initiation of CRRT (**Baseline)**	**12 hours**	**24 hours**	**36 hours**	**48 hours**	**60 hours**	**72 hours**	**HF20 CRRT End (if** between 12 hour visit intervals)
Heparin Use Only Labs									
Clotting Parameters Labs (PTT, APTT, ACT)		*	*	*	*	*	*	*	*
Citrate Use Only Labs									
Extracorporeal Circuit Calcium		As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	NA
Patient Ionized Calcium		As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care	NA
CRRT Treatment									
Treatment Prescription		X	X	X	X	X	X	X	
Priming Solutions		X	X	X	X	X	X	X	
Anticoagulation		X	X	X	X	X	X	X	
Dialysate		X	X	X	X	X	X	X	
CRRT Treatment Details		X	X	X	X	X	X	X	
Treatment Modality		X	X	X	X	X	X	X	
Record Bag Weights*		*	*	*	*	*	*	*	*
Record Syringe Volume *		X	X	X	X	X	X	X	X
Filter Changes		X	X	X	X	X	X	X	
Patient Weight	X	X		X		X		X	X

Assessment	**Up to 24 hrs prior to CRRT (Screening)**	**At initiation of CRRT (**Baseline)**	**12 hours**	**24 hours**	**36 hours**	**48 hours**	**60 hours**	**72 hours**	**HF20 CRRT End (if** between 12 hour visit intervals)
Fluid Overload Assessment[1]	X	X	X	X	X	X	X	X	X
Survival status								X	X
Protocol Deviations		X	X	X	X	X	X	X	X
AE	X	X	X	X	X	X	X	X	X
SAE	X	X	X	X	X	X	X	X	X
Con Meds	X	X	X	X	X	X	X	X	X
Alarms		X	X	X	X	X	X	X	X
** As per local std of care*		***Baseline labs are to be obtained within 1 hour prior to start of CRRT or within 15 minutes after start of CRRT*							

[1] [1] Degree of fluid overload= fluid intake(L)-fluid output (L)/ICU admission wt (kg) (×) 100%

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14. LIST OF APPENDICES

APPENDIX I	Statistical Plan

Appendix 1 Statistical Plan

Objective

The primary objective of the trial is to verify that the Prismaflex HF20 Set is able to deliver effective treatment in small patients. Its efficacy will be measured by the reduction in blood urea nitrogen (BUN). This will be measured every 12 hours at the start of, and during, treatment. Creatinine reduction and the TCO_2 profile will be assessed as secondary endpoints along with survival time of the Prismaflex HF20 Set out to 72 hours. [redacted]. A repeated measures ANOVA will be used to test TCO_2. No formal statistical analysis of the safety endpoint will be carried out; rather these events will be assessed for severity and device-relatedness, and reported in narrative form.

Primary Endpoint

The primary endpoint of analysis will be to demonstrate that a mean reduction of greater than 38% in BUN is seen at 24 hours from initiation of CRRT. This percentage reduction is motivated by the target of getting patients with an initial BUN of 80 mg/dL below 50 mg/dL after 24 hours of treatment.

The null hypothesis to be tested is

H_0: $\mu \leq 38$, vs

H_a: $\mu > 38$

Where μ stands for the mean percentage reduction in BUN from baseline to 24 hours.

Secondary Endpoints

A secondary endpoint will consist of testing whether there is a significant change in creatinine and TCO_2 from baseline to 24 hours. This will be done by turning the creatinine and TCO_2 readings into percent change from baseline and testing whether the percent change is significantly different from zero for each parameter. Another secondary endpoint is the survival time of the Prismaflex HF20 Set. The failure time of the Prismaflex HF20 Set, defined as when one of the following two alarms continues to

be triggered despite mitigation steps, “Warning: Filter Clotted”, and/ or "Caution: TMP Excessive", will be recorded and analyzed to determine the survival function of the filter set. Safety will also be investigated by reporting: AEs, SAEs, device deficiencies and alarms.

In addition, the mean concentrations of BUN, creatinine and TCO_2 will be computed, along with 95% confidence intervals, at baseline and at each subsequent 12-hour sampling time. [redacted]

Other Measures

Other patient and treatment measures will be captured during each patient’s treatment. Summary numbers for these measures (mean, standard deviation, minimum and maximum) will be reported for each time point at which the measure is made.

Statistical Analysis Plan

Analysis of Primary Endpoint

The primary endpoint for the reduction in BUN will be assessed using a one-sample t test.

The actual mean percentage reduction in BUN will be quantified using 95% confidence intervals.

As a supportive analysis, an analysis of variance (ANOVA) will be implemented to investigate the mean change from baseline among the different sites.

The Analysis of the primary endpoint will be carried out on both the FA and PP.

Analysis of Secondary Endpoints

The change from baseline in creatinine and TCO_2 will be analyzed as described above for the primary endpoint.

The survival time of the Prismaflex HF20 Set will be analyzed using a Kaplan Meier survival curve to generate the survival function of the filter set.

AEs, SAEs and Device Deficiencies will be summarized by seriousness, relationship to study device, severity and overall frequency. Fluid Flow Alarms will also be reported.

The secondary analysis will be carried out on the FA.

Exploratory Trend Analysis

[redacted]

Analysis Populations

Full Analysis Set (FA): The Full Analysis Set is based on the intent-to-treat principle and includes any patient who received CRRT on the Prismaflex HF 20 Set for any period of time.

Per-Protocol Analysis Set (PP): The Per-Protocol Analysis Set defines a subset of the FA including patients who

- fulfilled all inclusion criteria

- did not meet any of the exclusion criteria
- received at least 20 hours of CRRT treatment on the Prismaflex HF20 Set with no more than 1 interruption which may have included a filter change.
- did not have major protocol deviations that might impact the assessment of the primary endpoint
- have available measurements for the primary endpoint (BUN) at baseline (within 1 hour prior, and 15 min after initiation of CRRT) and at 24 hours (±1 hour) from start of CRRT

Dropout

The primary endpoint is assessed at 24 hours, with a baseline reading within one hour prior to CRRT initiation and within 15 minutes after start of CRRT, patients are allowed one interruption which may include a filter change lasting up to 4 hours. Patients with an interruption lasting more than 4 hours or with a second Prismaflex HF20 Set change will be excluded from the PP.

Sample Size

The sample size calculation is based on the primary objective of 24-hour BUN reduction. It is anticipated that the true mean reduction at 24 hours will be some 62%, as would be obtained from a patient with initial BUN of 80 mg/dL and reaching 30 mg/dL after 24 hours of treatment. Data from the earlier M-10 study suggest that the standard deviation in the BUN reduction is about 45%.

Under these assumptions, the sample size needed to obtain 80% power is 24, as reported by SAS PROC POWER.

A target sample size of up to 30 patients is therefore proposed to allow for a possible 20% loss of data between the baseline and 24 hour marks.