Statistical Analysis Plan: 1463

Study Title:	Clinical Evaluation of the Prismaflex® HF20 Set and Prismaflex System 7.10 for Acute Continuous Renal Replacement Therapy (CRRT) in Children
Study Number:	1463
Study Phase:	Not Applicable
Study Design	Multicentric, open label, single group study
Product Name:	Prismaflex HF20 Set and Prismaflex System Software Version 7.10 or Prismaflex HF20 Set and Prismaflex System Software Version 7.20
Indication:	Acute Kidney Injury treated with CRRT
Statistician:	[redacted] [redacted] Baxter Healthcare One Baxter Parkway Deerfield, IL 60015
Sponsor:	Baxter Healthcare Corporation One Baxter Pkwy Deerfield, Illinois 60015
Responsible Medical Officer:	[redacted], M.D, Ph.D. [redacted] Baxter Healthcare Corporation
Final Date:	2018 MAY 30
Version:	1.0

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1. SIGNATURE PAGE

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

Study Number: 1463

Statisticians: [redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Prepared by: [redacted] Date: [redacted]

Baxter Healthcare Corporation

Approved by: [redacted] Date: [redacted]

Baxter Healthcare Corporation

Approved by: [redacted] Date: [redacted]

Baxter Healthcare Corporation

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACT	Activated Clotting Time
ADE	Adverse Device Event
AE	Adverse Event
AKI	Acute Kidney Injury
APTT	Activated Partial Thromboplastin Time
ANOVA	Analysis of Variance
B2M	Beta 2 Microglobulin
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CI	Confidence Interval
Cr	Creatinine
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
FUN	Fluid Urea Nitrogen
g/dl	Grams per Deciliter
GCP	Good Clinical Practices
hr	Hour
HGB	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
ICU	Intensive Care Unit
ITT	Intent-to-treat
IRB	Institutional Review Board
kg	Kilograms
KDIGO	Kidney Disease Improving Global Outcomes

L	Liter
lbs	Pounds
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
mg	Milligram
min	Minute
ml	Milliliter
mmHg	Millimeters of Mercury
PBP	Pre-Blood Pump
PICU	Pediatric Intensive Care Unit
PPS	Per Protocol Set
PTT	Partial Thromboplastin Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
t	time (may appear in multiple formats [e.g., t'] as it can designate different time periods like "time since drug administration" or "time of infusion"
TCO_2	total carbon dioxide: CO_2 in physical solutions or loosely bound to proteins, bicarbonate ($HC0_3$) or carbonate (CO_3) anions, and carbonic acid (H_2CO_3).
TMP	Transmembrane Pressure
US	United States

3. INTRODUCTION

The statistical analysis plan (SAP) is created based on study Protocol 1463 Amendment 6.1 dated 06 December 2017.

This SAP describes the patient populations that will be analyzed, the variables that will be used for the analyses and the statistical methods that will be employed, which, will be used to guide statistical programming. The intention of the SAP is to expand on the details of the planned statistical methods described in the study protocol.

4. TRIAL OBJECTIVES

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.[1,2] Software Version 7.10 and Version 7.20 of the Prismaflex have been developed to safely treat children weighing down to 8 kg with respect to fluid balance.

4.1 Primary Objectives

The primary objective of this study is to evaluate the efficacy of the Prismaflex HF20 Set based on testing the hypothesis that it delivers sufficient renal replacement therapy (>38% reduction of Blood Urea Nitrogen (BUN) from baseline to 24 hours) to effectively treat Acute Kidney Injury (AKI) in pediatric patients weighing ≥8 and <20 kg (ie, ≥17.6 and <44.09 lbs).

4.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of removing creatinine and normalizing bicarbonate.
- 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.

4.3 Exploratory Objectives

[redacted]

[redacted]

5. STUDY DESIGN AND CONDUCT CONSIDERATIONS

5.1 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 the study protocol, and deemed treatable by their physician with the Prismaflex HF20 Set and Prismaflex System Software Version 7.10 or with the Prismaflex HF20 Set and Prismaflex System Software Version 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.

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 patient has been on the current Prismaflex HF20 Set for less than 72 hours, the patient is allowed to continue on their current filter set until the end of filter life (please refer to the study Protocol Section 3.2 for explicit detail). The site may follow applicable institutional practices if additional CRRT is required.

5.1.1 Baseline Definition

All baseline values will be collected during the study visit in which study CRRT treatment is initiated. Baseline measure for laboratory assessments is defined as within 1 hour prior to or within 15 minutes after the initiation of CRRT.

Baseline values for BUN will be utilized in the primary endpoint analysis while creatinine and bicarbonate baseline values will be utilized in the secondary endpoint analysis.

5.2 Sample Size

The sample size calculation is based on the primary objective of 24hours 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 hours mark.

5.3 Randomization Procedure

This study is not randomized as all patients will be treated with the Prismaflex HF20 Set and Prismaflex System Software Version 7.10 or Prismaflex HF20 Set and Prismaflex System Software Version 7.20.

5.4 Schedule of Visits and Procedures

The schedule of events is presented below in Table 1.

Table 1 Schedule of Events

Assessment	Up to 24 Hours 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 hours 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 GUI 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 (from GUI 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)
Medical & Surgical History	X								
Diagnosis	X								

Assessment	Up to 24 Hours 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 hours intervals)
General Labs	Up to 24 hr prior	(Within 1 hr prior to or within 15 min 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 hours 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	*	*	*	*	*	*	*	

Assessment	Up to 24 Hours 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 hours intervals)
Heparin Use Only Labs									
Clotting Parameters Labs (PTT, APTT, ACT)		*	*	*	*	*	*	*	*
Citrate Use Only Labs									
Extracorporeal Circuit Calcium		*	*	*	*	*	*	*	
Patient Ionized Calcium		*	*	*	*	*	*	*	
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		*	*	*	*	*	*	*	*

Assessment	Up to 24 Hours 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 hours intervals)
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
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 determined by local standard 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 assessment = fluid intake(L)-fluid output (L)/ICU admission weight (kg) (×) 100%

5.5 Efficacy Measures

5.5.1 Primary Efficacy Measures

The primary efficacy endpoint is the change from baseline in BUN evaluated at 24 hours following initiation of CRRT with the Prismaflex HF20 Set. BUN is to be measured at the start of CRRT treatment with the Prismaflex System, specifically BUN measurements will be taken no earlier than one hour prior to the start of CRRT and no later than 15 minutes after the start of CRRT. BUN will also be measured at 24 hours after initiation of CRRT. More specifically, BUN will be measured no later than one hour after 24 hours past CRRT initiation (25 hours treatment mark) and no sooner than one hour before 24 hours after CRRT initiation (23 hours mark). Change in baseline of BUN to 24 hours after CRRT initiation will be calculated as a percentage using the following equation:

$$\Delta\text{BUN} = \frac{\text{BUN}_{0hr} - \text{BUN}_{24hr}}{\text{BUN}_{0hr}} \times 100\%$$

Where BUN_{0hr} is BUN recorded at baseline and BUN_{24hr} is BUN recorded at 24 hours after CRRT initiation.

5.5.2 Secondary Efficacy Measures

Creatinine and bicarbonate measurements will be collected according to the same time schedule and assessment windows as given above for BUN and used in a change from baseline analysis calculated as a percentage in the same manner as for BUN.

Change in baseline of creatinine to 24 hours after CRRT initiation will be calculated as a percentage using the following equation:

$$\Delta\text{Cr} = \frac{\text{Cr}_{0hr} - \text{Cr}_{24hr}}{\text{Cr}_{0hr}} \times 100\%$$

Where Cr_{0hr} is creatinine recorded at baseline and Cr_{24hr} is creatinine recorded at 24 hours after CRRT initiation.

Change in baseline of TCO_2 to 24 hours after CRRT initiation will be calculated as a percentage using the following equation:

$$\Delta\text{TCO}_2 = \frac{(\text{TCO}_2)_{0hr} - (\text{TCO}_2)_{24hr}}{(\text{TCO}_2)_{0hr}} \times 100\%$$

Where $(TCO_2)_{0hr}$ is TCO_2recorded at baseline and $(TCO_2)_{24hr}$is TCO_2 recorded at 24 hours after CRRT initiation.

[redacted]

Another secondary endpoint for this study is to analyze the extracorporeal circuit life of the Prismaflex HF20 Set. The clock time of treatment initiation will be recorded along with the clock time of when the patient is taken off of the Prismaflex HF20 Set. The circuit life of the filter will be determined by the duration of time between these two measurements. If the patient has an interruption and is taken off the filter during the first 24 hours of the treatment, the clock time of the treatment interruption start and end will be recorded and subtracted from the total time on the Prismaflex HF20 Set. If the patient has an interruption and is started on a new filter, then the clock time of the CRRT initiation on the new filter will be recorded and this will serve as the start time of the patient's filter.

5.6 Safety Measures

While no formal primary safety analysis is planned for this study, one of the secondary endpoints is the safety of the Prismaflex System in pediatric AKI patients. Adverse Events (AEs) and Serious Adverse Events (SAEs) along with device deficiencies will be continuously collected throughout the study (up to 72 hours after treatment initiation on the final HF20 Set).

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

- "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.

Fluid overload will also be calculated and reported at baseline and every 12 hours after until treatment completion.

Patient CRRT treatment prescription will be recorded at CRRT initiation and at the beginning of each visit window (every 12 hours) for up to 72 hours. Values recorded will include: CRRT modality, blood prime used, CRRT anticoagulation, blood flow rate, pre-blood pump flow rate, PBP brand name/manufacturer, PBP formulation, dialysate flow rate, dialysate brand name/manufacturer, dialysate formulation, post filter replacement flow rate, post filter fluid formulation, use of anticoagulation, anticoagulation formulation and anticoagulation rate.

Patient CRRT values will be collected every hour and include: TMP, prescribed patient fluid removal rate, actual period fluid removal, total fluid removal, actual unintended patient fluid gain/loss, prescribed unintended patient fluid gain/loss, and prescribed effluent rate.

Post treatment outcome data will be collected upon the completion of study CRRT and includes: Pediatric Intensive Care Unit (PICU) outcome, total prescribed dose, total delivered dose, dry weight and metabolic control attained and the patient's survival status.

Lab values will be collected at screening and CRRT initiation and will be taken every 12 hours for up to 72 hours after CRRT initiation. Any lab values which are considered abnormal clinically significant will be recorded as an adverse event.

Vital signs will be collected at screening and CRRT initiation and will be taken every hour for up to 72 hours after CRRT initiation. Any vital which is considered abnormal and clinically significant will be recorded as an adverse event.

Heparin anticoagulation use, citrate anticoagulation use and HGB/total calcium monitoring will be observed and recorded throughout the entirety of this study along with any medication taken by the patient.

5.7 Pharmacokinetic Parameters

Not applicable.

5.8 Completion and Discontinuation

Patients are considered withdrawn from the study if their participation is discontinued before completion of the required evaluations as described in the study protocol. Patients may be withdrawn for any of the following reasons:

- Adverse Event (AE)
- Lack of efficacy
- Non-Compliance with Study Treatment
- Protocol Violation
- Withdrawal of Consent
- Lost to follow-up
- Other (with reason noted)

The investigator may terminate a patient's study participation at any time during the study if he/she judges it to be in the patient's best interest. If a patient is withdrawn from the study, the Clinical Study Manager should be informed at the earliest possible opportunity, regardless of the reason of withdrawal. In addition, a patient may discontinue his or her participation at any time during the study without having to justify their decision. If a patient's participation is discontinued, the reason(s) must be recorded in the source documents and on the electronic case report form (eCRF). If a patient discontinues for any reason, every effort should be made to perform all the procedures that are scheduled for the End of Study Visit. In addition, serious adverse events (SAEs) and adverse device events (ADEs) related or not, will be followed post-study according to the safety plan.

6. STUDY POPULATIONS

The study population consists of pediatric patients with Acute Kidney Injury (AKI) treated with continual renal replacement therapy (CRRT). Approximately 30 patients will be enrolled.

Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled 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 will be defined as either 1) Acute Kidney Injury 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 rise in 48 hours, or 2) as AKI as defined by the Pediatric modified Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) criteria which is a 25% reduction in estimated creatinine clearance, OR 3) a serum creatinine ≥1.2 mg/dL.

   OR

   Patients with severe fluid overload, defined as a ≥10% Intensive Care Unit (ICU) fluid accumulation (based on ICU admission weight) will be included in the study (% fluid accumulation – [(Fluids in (liters) – Fluid Out (liters)/ICU admit weight (kg) *100%] and BUN ≥ 40mg/dL.

3. Patients who have received renal replacement therapy previously can be included in the study if >72 hours have elapsed since previous RRT provision.
4. Provide written informed consent form one or both parents as required by the local IRB or a legal guardian 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 CRF Part 50.55(e).

Exclusion Criteria

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

1. The following hemoglobin exclusion criteria apply:

Weight	Starting HGB (g/dL)	Exclusion Criteria
8.0-20.0 kg	<7.0	Excluded with blood prime
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.

6.1 Patient Disposition

A summary will be generated to provide the number and proportion of patients who were screened and who were screen failures (including the reason for screen failure) as well as those patients in the full analysis set (FAS) and per-protocol analysis set (PPS) and those patients who completed the study or prematurely discontinued. A further breakdown will be provided regarding the reasons for premature discontinuation as documented on the patient disposition eCRF. As well as a flowchart of patient disposition will be provided.

6.2 Analysis Populations

The full analysis set (FAS) is based on the intent-to-treat (ITT) principle and includes any patient who received CRRT on the Prismaflex HF20 Set for any period of time.

The Per-Protocol Analysis Set (PPS) is a subset of the FAS 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 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

6.3 Protocol Deviations

Protocol deviations will be classified as minor or major deviations (as determined by the Baxter Medical Monitor) and reviewed at a data review meeting.

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

The total number of major and minor protocol deviations and the number of patients having at least one major or minor protocol deviation will be tabulated for each analysis population.

6.4 Subgroups

If applicable, the HF20 Sets with lower clearance specifications (KUrea = 25.5 mL/min +/- 10%) and the HF20 Sets with higher clearance specifications (KUrea = 30 mL/min +/- 10%), will be considered as two subgroups for the analysis of BUN reduction.

7. STATISTICAL ANALYSIS

7.1 General/Types of Analyses

Unless otherwise noted, all analyses will be performed using SAS/GRAPH® 9.4 software, SAS/STAT® 14.1 software and Base SAS® 9.4 software.

Unless otherwise specified, treatment effects will be evaluated on the basis of a 2-sided significance level of 0.050 (when rounded to three decimal places).

7.2 Handling of Missing Data

The sensitivity analyses will be performed using a multiple imputation approach. Multiple imputations using SAS PROC MI will be implemented to impute missing data under the missing at random assumption and the data sets generated will be analyzed using SAS PROC MIANALYZE.

The multiply imputed data sets are then analyzed by using standard procedures for complete data and combining the results from these analyses. Multiple imputation does not attempt to estimate each missing value through simulated values, but rather to represent a random sample of the missing values. This process results in valid statistical inferences that properly reflect the uncertainty due to missing values.

Multiple imputation inference involves three distinct phases:

1. The missing data are filled in m times to generate m complete data sets.
2. The m complete data sets are analyzed by using standard procedures.
3. The results from the m complete data sets are combined for the inference.

The MI procedure is a multiple imputation procedure that creates multiply imputed data sets for incomplete p-dimensional multivariate data. It uses methods that incorporate appropriate variability across the m imputations. The imputation method of choice depends on the patterns of missingness in the data and the type of the imputed variable.

Twenty (20) complete data sets based on the Markov chain Monte Carlo (MCMC) method with pre-specified covariates (age and gender) will be analyzed for the multiple imputation of the primary endpoint data as sensitivity analysis.

Three additional imputation approaches will be carried out:

1. Imputing the mean of the available data.
2. Imputing the missing values by estimating the values from a linear regression on the available data.
3. Imputing by worst-case approach, using the smallest observed reduction from baseline to 24 hours in BUN measurement.

7.3 Interim Analysis

No interim analysis is planned for this study.

7.4 Pooling Strategy for Study Sites

With an overall study sample size of 30 patients distributed among six to ten study sites, the ideal distribution of patients is three to five patients in each study site.

For the purpose of the analysis of variance (ANOVA) for the primary and secondary endpoints, study sites with 3 or less patients will be combined in a way that the resulting study sites utilized in the analysis have similar patient numbers.

7.5 Visit Windows/Unscheduled Visits

All patients will be screened up to 24 hours prior to treatment. Treatment will consist of one CRRT session lasting no longer than 72 hours from the start of study treatment. For a detailed description of visit windows please reference Table 1 Schedule of Visits and Procedures as well as Table 2 Blood Sampling Schedule and Table 3 Vital Signs and Fluid Overload Assessment Schedule. Unscheduled visits, while not anticipated, will be considered for analysis depending on purpose and time point of measurement.

Table 2. Blood Sampling Schedule

Solute	Prior to CRRT*	At Initiation of CRRT**	During CRRT	End of HF20 CRRT (if after 24 hours & between 12 hours 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 1 hour prior to or within 15 minutes after CRRT initiation.	At +/- 1 hour of 12, 24, 36, 48, 60 and 72 hours	Use previous 12 hours interval result
FUN	N/A	Within 1 hour prior to or within 15 minutes after CRRT initiation.	At +/- 1 hour of 12, 24, 36, 48, 60 and 72 hours	Use previous 12 hours interval result
Creatinine	Up to 24 hours prior to initiation of CRRT	Within 1 hour prior to or within 15 minutes after CRRT initiation.	At +/- 1 hour of 12, 24, 36, 48, 60 and 72 hours	Use previous 12 hours interval result
Bicarbonate	Up to 24 hours prior to initiation of CRRT	Within 1 hour prior to or within 15 minutes after CRRT initiation.	At +/- 1 hour of 12, 24, 36, 48, 60 and 72 hours.	Use previous 12 hours interval result
Sodium	Up to 24 hours prior to initiation of CRRT	Within 1 hour prior to or within 15 minutes after CRRT initiation.	At +/- 1 hour of 12, 24, 36, 48, 60 and 72 hours	Use previous 12 hours interval result
Potassium	Up to 24 hours prior to initiation of CRRT	Within 1 hour prior to or within 15 minutes after CRRT initiation.	At +/- 1 hour of 12, 24, 36, 48, 60 and 72 hours	Use previous 12 hours interval result
Chloride	Up to 24 hours prior to initiation of CRRT	Within 1 hour prior to or within 15 minutes after CRRT initiation.	At +/- 1 hour of 12, 24, 36, 48, 60 and 72 hours	Use previous 12 hours interval result
Phosphorous	Up to 24 hours prior to initiation of CRRT	Within 1 hour prior to or within 15 minutes after CRRT initiation.	At +/- 1 hour of 12, 24, 36, 48, 60 and 72 hours	Use previous 12 hours interval result
Albumin	Up to 24 hours prior to initiation of CRRT	Within 1 hour prior to or within 15 minutes after CRRT initiation.	At +/- 1 hour of 12, 24, 36, 48, 60 and 72 hours	Use previous 12 hours interval result
B2M	N/A	Within 1 hour prior to or within 15 minutes after CRRT initiation.	At +/- 1 hour of 24,48, and 72 hours	Use previous 12 hours interval result

Solute	Prior to CRRT*	At Initiation of CRRT**	During CRRT	End of HF20 CRRT (if after 24 hours & between 12 hours interval)
ACT (Applies to heparin use only)	N/A	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)	N/A	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)	N/A	As determined by local standard of care	As determined by local standard of care	As determined by local standard of care
Total Calcium	N/A	As determined by local standard of care	As determined by local standard of care	N/A
Extracorporeal Circuit ionized calcium (Not indicated when heparin or no anticoagulation are used)	N/A	N/A	As determined by local standard of care	N/A
Patient Ionized Calcium (Not indicated when heparin or no anticoagulant are used)	N/A	N/A	As determined by local standard of care	N/A

* 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 3. Vital Signs and Fluid Overload Assessment Schedule

Parameter	Prior to CRRT	At Initiation of CRRT - Baseline	During CRRT	End of CRRT (& if prior to 72 hours)
BP (mmHg)	Within 24 hours prior to CRRT	Within 1 hour prior to or within 15 minutes after CRRT Initiation	Hourly (± 15 minutes)	End of Treatment (± 15 minutes)
MAP (mmHg)	Within 24 hours prior to CRRT	Within 1 hour prior to or within 15 minutes after CRRT Initiation	Hourly (± 15 minutes)	End of Treatment (± 15 minutes)
Degree of Fluid Overload*	Within 24 hours prior to CRRT	Within 1 hour prior to or within 15 minutes after CRRT Initiation	At +/- 1 hour of 12, 24, 36, 48, 60, & 72 hours	End of Treatment (± 15 minutes)

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

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

7.6 Other Issues

Not applicable.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized using descriptive statistics for all subjects as well as for each clearance specification subgroups (if applicable).

Demographic data include age, gender, race, ethnicity, height, weight at hospital admission, body surface area and calculated intravascular blood volume. Calculated intravascular blood volume will be calculated as 70 ml multiplied by the patient's hospital admission weight in kilograms.

Baseline characteristics collected on the eCRF also include medical history and acute kidney injury history. Acute kidney injury (AKI) history recorded data will include: cause of AKI, current ICU diagnosis, prior CRRT treatment, and end date and time of last CRRT treatment.

Lab data including: serum sodium, potassium, chloride, bicarbonate, serum creatinine, phosphorus, total calcium, albumin, beta 2 microglobulin, BUN, and FUN are collected at baseline as well as at screening and every 12 hours for up to 72 hours after CRRT initiation. Vital sign data including: temperature, systolic/diastolic blood pressure, mean arterial pressure, pulse, and respiratory rate are captured at baseline as well as screening and hourly up to 72 hours after CRRT initiation. Mechanically ventilated patients will also be recorded every 12 hours after initiation of CRRT.

The following describes the summary of various types of demographic and baseline data either as continuous data, frequency tabulations or as listings:

1. Age, height, hospital admission weight, body surface area, and calculated intravascular blood volume will be summarized as a continuous variable.
2. The frequencies for gender, race and ethnicity will be tabulated.
3. Medical conditions and surgery items recorded in the medical history eCRF will be coded to a Medical Dictionary for Regulatory Activities (MedDRA, Version 16.1 or higher) and listed by system organ class and preferred term
4. AKI history will be listed for each patient.
5. All laboratory samples collected at baseline will be summarized as continuous variables for both analysis populations.

6. All vital sign values collected at baseline will be summarized as continuous variables populations except for the number of patients mechanically ventilated at baseline which will be presented as a frequency and percentage.

Continuous data will typically be summarized using the number of patients (n), mean, standard deviation, minimum, median, and maximum, while categorical data will be presented by frequency count and percentage.

9. ANALYSIS OF PHARMACOKINETICS AND PHARMACODYNAMICS

Not applicable.

10. TREATMENT COMPLIANCE AND EXPOSURE

Treatment compliance will be provided in listings and summarized as a frequency of both, patients that started CRRT, and those patients which had a measurement taken at the 24 hours time point. The patients with both baseline and 24 hours time point measurements will also be summarized as frequency counts. The total time of CRRT will also be summarized as a continuous variable for both population sets. Treatment compliance and exposure will be summarized for both the Full Analysis Set and Per Protocol Set.

11. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

All the changes in the planned analysis have been agreed upon Baxter and the FDA in a pre-submission meeting on February 27, 2018:

- Subgroup analysis will be added due to the HF20 Set used in this study may have two specification limits. (See Section 12.6 for explicit details.)
- Missing data imputation will be performed. (See Section 7.2 for explicit details.)
- Primary endpoint will use the FAS as primary analysis; and use the PPS as supportive analysis. (See Section 12.1 and Section 12.2 for explicit details.)
- Statistical testing for the 24 hours percentage reductions of creatinine and bicarbonate from baseline will be removed.

12. EFFICACY PARAMETERS

12.1 Primary Analysis

The primary analysis will be to demonstrate a mean reduction of greater than 38% in BUN at 24 hours from initiation of CRRT. This percentage of 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 hypothesis to be tested is:

H_0: $\mu \leq 38\%$,

H_a: $\mu > 38\%$

Where μ stands for the mean percentage reduction in BUN from baseline to 24 hours calculated as:

$$\mu = \frac{\mathrm{BUN}_{0hr} - \mathrm{BUN}_{24hr}}{\mathrm{BUN}_{0hr}} \times 100\%$$

Where BUN_{0hr} is BUN recorded at baseline and BUN_{24hr} is BUN recorded at 24 hours after CRRT initiation.

This hypothesis will be tested using a one-sample t test and the actual mean percentage reduction in BUN will be quantified using a 95% confidence interval.

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

A box plot will also be generated to represent the 24 hours change in BUN from baseline.

The primary analysis of the primary endpoint will be based on the FAS. As supportive analysis, the same analysis will be carried out on the PPS.

12.2 Sensitivity Analysis

The analysis of the primary endpoint using the PPS will be considered as a part of sensitivity analyses.

Subgroup analysis (if applicable) will be also considered as a part of sensitivity analyses.

The impact of missing data on the primary analysis will be further explored as sensitivity analyses using statistical imputation approaches. (See Section 7.2 for explicit details.)

12.3 Secondary Analysis

The percent change from baseline to 24 hours after treatment initiation in creatinine and TCO_2 will be summarized descriptively.

The survival time of the Prismaflex HF20 Set will be analyzed using a Kaplan Meier survival curve to generate the median (0.50), 1st (0.75) and 3rd (0.25) quartile survival times after the start of CRRT.

The life of a filter that is replaced due to continuous use for 72 hours will be censored for the statistical analysis of this secondary endpoint. Filters that are replaced any time CRRT is stopped for reasons other than the failure to medicate the two alarms specified in Section 5.1 will be censored at their current duration of usage. Only filters that are replaced due to the two alarms (filter clotted, and TMP excessive) shall be considered events for this survival analysis.

Box plots will also be generated to represent the 24 hours percent change in creatinine and TCO_2 from baseline.

The secondary analysis will be carried out on the FAS and PPS.

12.4 Exploratory Analyses

[redacted]

12.5 Interim Analysis

There is no interim analysis planned for this study.

12.6 Subgroup Analyses

If applicable, for each subgroup, the HF20 sets with lower clearance specifications (KUrea = 25.5 mL/min +/- 10%) and the HF20 sets with higher clearance specifications (KUrea = 30 mL/min +/- 10%), descriptive statistics will be carried out for the reduction in BUN, creatinine and bicarbonate from baseline to 24 hours.

13. SAFETY AND TOLERABILITY

13.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

An overview of the number of patients with at least one Adverse Event (AE) (serious or non-serious), and at least one Serious Adverse Event (SAE) will be tabulated. This overview will also include the number of patients meeting each of the individual serious criteria and the number of patients related to either: study filter, device or study therapy for AEs (serious or non-serious) and SAEs as well as the number of patients with an AE (serious or non-serious) or SAE which led to a change in medication, device interruption, device withdrawal or discontinuation of the study. The overall number of AEs (serious or non-serious) will also be tabulated. The number of patients with at least one AE (serious or non-serious) and at least one SAE will be presented by MedDRA system organ class and preferred term. The number of AEs (serious or non-serious) and SAEs will be presented by MedDRA system organ class and preferred term; counts and rate of AEs or SAEs per patient treatment day will also be provided.

The number of patients with at least one AE (serious or non-serious) or SAE will be tabulated by diagnosis and severity (mild, moderate, and severe). The total number of AEs (serious or non-serious) and SAEs will also be tabulated by severity.

AEs (serious or non-serious) and SAEs will also be presented by patient and by total number of events by system organ class, preferred term and relationship to Prismaflex System, HF20 Set and study therapy.

Medication taken to treat AEs and SAEs will be tabulated by indication and brand name.

Any patient-based analysis of AEs (eg, number of patients with at least one AE) will be based on the worst severity reported for the patient for the event analyzed. If, for example, a patient reports two mild and one moderate AEs within the same system organ class and preferred term, in the patient-based analysis, the event will be presented only once under moderate severity. Prismaflex System related AEs, HF20 Set related AEs and study therapy related AEs will be considered as those AEs classified as related or possibly related with the system, filter or treatment. AEs unrelated to study system, filter or treatment will be considered those with causality assessment of not related or unlikely

related. If the relationship to the filter, system or therapy is not available or not assessable, the respective AE will be classified as system, filter or study therapy related respectively.

Data listings for AEs and SAEs will contain AE term, start date, stop date, severity, seriousness, relationship to system, relationship to filter, relationship to therapy, action taken, action taken with CRRT, and outcome.

Data listings will also be generated for AEs that caused the patient to withdraw from the study, as well as those AEs that lead to death.

Adverse events reported between signing the Informed Consent Form (ICF) and first study treatment will be listed separately.

13.2 Device Deficiencies/Alarms

The total number of patients who experienced a device deficiency or an alarm will be tabulated along with the total number of device deficiencies and alarms.

A summary listing of all device deficiencies and alarms will also be generated by patient.

The tabulated values will be presented for both the FAS and PPS. The listings will only be generated for the FAS.

13.3 Laboratory Values

Any abnormal laboratory results will be reported as adverse events if deemed clinically significant by the primary investigator. Summary tables and listings for all laboratory values at all time points will be generated and will include change from baseline values for all post baseline time points. Shift tables will also be generated to analyze any changes from baseline in low, normal or high ranged values. All lab values will be summarized as continuous values utilizing: minimum, maximum, median, mean and standard deviation along with the number of observations analyzed. All labs for all time points will also be listed by patient.

Laboratory values will be summarized and listed for the Full Analysis Set only.

13.4 Vital Signs

Any abnormal vital sign values will be reported as adverse events if deemed clinically significant by the primary investigator. Summary tables will be generated for all recorded time points of all vital sign parameters and will include change from baseline for post baseline time points. Shift tables will also be generated to analyze any changes

from baseline in low, normal or high vital sign values. All vital sign values will be summarized as continuous values utilizing: minimum, maximum, median, mean and standard deviation along with the number of observations analyzed. All vital signs for all time points will be listed for all patients.

Summary tables and listings for vital signs will be provided for the FAS only.

13.5 Fluid Overload

Calculated patient fluid overload will be summarized as a continuous variable for all time points across all patients and will also be listed by patient and time point. Fluid overload is calculated as: fluid intake (L)-fluid output (L)/ICU admission weight (kg) (×) 100%

Summary tables and listings for fluid overload will be provided for the FAS only.

13.6 CRRT Prescription Values

All CRRT prescription values will be listed by patient for the FAS.

13.7 CRRT Values

All CRRT recorded values will be summarized by minimum, maximum, median, mean and standard deviation for continuous variables or as frequency counts for categorical variables. CRRT Values will also be listed by patient and by time point.

CRRT values will be summarized for the FAS only.

13.8 Post Treatment Outcome Data

Post treatment outcome data will be summarized as continuous variables (except PICU outcome, dry weight attained, metabolic control attained, and death, which will be tabulated as frequencies) across all patients and will also be listed by patient. Continuous variables will be presented by minimum, maximum, median, mean and standard deviation.

Post treatment outcome data will be summarized for the FAS only.

13.9 Anticoagulation, HGB and Total Calcium Monitoring

Specifications for heparin anticoagulation, citrate anticoagulation, and HGB and total calcium monitoring will be listed by patient and time of use for the FAS.

13.10 Concomitant Medications

Any medication taken by the patient during the study will be coded to the WHO drug dictionary and will be summarized in frequency tables and patient listings.

All concomitant medication summaries will be conducted on the FAS.

14. OTHER RELEVANT DATA ANALYSES/SUMMARIES

Not applicable.

15. REFERENCES

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3. Goldstein SL. Hemodialysis in the Pediatric Patient: State of the Art. *Adv Ren Replace Ther*. 2001;8(3):173-179.

4. Rubin, D. B. (1987). *Multiple Imputation for Nonresponse in Surveys* (pp. 166-167). New York: John Wiley & Sons.

5. *SAS/STAT® 14.1 User's Guide the MI Procedure* [PDF]. (2015, July). Cary, North Carolina: SAS Institute Inc.

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Statistical Analysis Plan: 1463

Study Title:	Clinical Evaluation of the Prismaflex® HF20 Set and Prismaflex System 7.10 for Acute Continuous Renal Replacement Therapy (CRRT) in Children
Study Number:	1463
Study Phase:	Not Applicable
Study Design	Multicentric, open label, single group study
Product Name:	Prismaflex HF20 Set and Prismaflex System Software Version 7.10 or Prismaflex HF20 Set and Prismaflex System Software Version 7.20
Indication:	Acute Kidney Injury treated with CRRT
Statistician:	[redacted] [redacted] Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015
Sponsor:	Baxter Healthcare Corporation One Baxter Pkwy Deerfield, Illinois 60015
Responsible Medical Officer:	[redacted], M.D, Ph.D. [redacted] Baxter Healthcare Corporation
Final Date:	2018 AUG 02
Version:	1.0 Amendment 1

[redacted]

[redacted]

1. SIGNATURE PAGE

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

Study Number: 1463

Statisticians: [redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Prepared by: [redacted] Date: [redacted]

[redacted]

Baxter Healthcare Corporation

Approved by: [redacted] Date: [redacted]

[redacted]

Baxter Healthcare Corporation

Approved by: [redacted] Date: [redacted]

[redacted], MD, PhD

[redacted]

Baxter Healthcare Corporation

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