Clinical Trial Protocol: 7905001, Amendment 5

Study Title:	A Multi-Center, Prospective, Randomized, Controlled, Open-label, Parallel Study to Evaluate the Safety and Efficacy of the Theranova 400 Dialyzer In End Stage Renal Disease (ESRD) Patients
Study Number:	7905001
Study Phase	Not Applicable
Product Name:	Theranova 400 Dialyzer
IDE Number:	G170157
Indication:	Theranova dialyzers are indicated for treatment of chronic and acute renal failure by dialysis. This study is intended to support an indication for expanded hemodialysis to remove middle molecular uremic toxins.
Investigators:	Multi-center
Sponsor:	Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015
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Original Protocol:	2017 JUN 12
Amendment 1:	2017 JUL 25
Amendment 2	2017 AUG 31
Amendment 3	2017 OCT 11
Amendment 4	2017 OCT 25
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Confidentiality Statement

Table of Contents

List of In-Text Tables

List of In-Text Figures

List of Appendices

SYNOPSIS

Sponsor:

Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, IL 60015

Name of Finished Product:
Theranova 400 Dialyzer

Comparator Product:
Elisio-17H Dialyzer

Study Title:
A Multi-Center, Prospective, Randomized, Controlled, Open-label, Parallel Study to Evaluate the Safety and Efficacy of the Theranova 400 Dialyzer In End Stage Renal Disease (ESRD) Patients

Study Number:
7905001

Study Phase:

Not Applicable

Primary Objective(s):
The primary efficacy objective of this study is to demonstrate that the Theranova 400 dialyzer has performance superiority to the Elisio-17H dialyzer in removing lambda immunoglobulin free light chains (λ FLCs).

The primary safety objective of this study is to demonstrate that performance of the Theranova 400 dialyzer compared to the Elisio-17H dialyzer is non-inferior, in regards to maintaining pre-dialysis serum albumin.

Secondary Objective(s):
The secondary objectives of this study are to evaluate the performance of the Theranova 400 dialyzer compared to the Elisio-17H dialyzer in removing serum middle molecules, dialysis adequacy, levels of coagulation factors, and characterize monthly trends in pre-dialysis serum albumin levels.

Study Design:
This is a multi-center, prospective, randomized, controlled, open-label, parallel study to evaluate medically stable end stage renal disease (ESRD) patients receiving dialysis treatment with either the Theranova 400 dialyzer or the Elisio-17H dialyzer for 3 sessions weekly, over 24 weeks.

Study Population:
The study population consists of subjects with ESRD who have been stable and receiving hemodialysis (HD) therapy at least 3 times a week for 3 months prior to enrollment. A sufficient number of patients will be enrolled in the study in order to randomize one hundred and sixty-six (166) patients in a 1:1 manner to either Theranova 400 dialyzer or the Elisio-17H dialyzer. The study will be conducted in up to thirty (30) study centers in the USA.

Test Product and Mode of Administration:
Theranova 400 dialyzer, a medium cut-off dialyzer.

Duration of Treatment:
Up to 24 weeks.

Efficacy Assessments:
The primary efficacy endpoint is the Reduction Ratio (RR) of λ FLC after 24 weeks of treatment.

Secondary efficacy endpoints include:

- Reduction ratio of λ FLC measured on the first day of treatment and after 4 weeks of treatment.

- Reduction ratio of complement factor D (CFD; MW = 27 kDa), κ FLC (MW = 23 kDa), interleukin 6 (IL-6; MW = 25 kDa), tumor necrosis factor alpha (TNFα; MW = 51 kDa), and β_2-microglobulin (MW = 11.6 kDa) measured after 4 weeks and after 24 weeks of treatment.
- Change in pre-dialysis β_2-microglobulin measured on the first day of treatment and after 24 weeks of treatment.
- Kt/V_{urea} measured after every 4 weeks of treatment.

Safety Assessments:
The primary safety endpoint is the pre-dialysis serum level of albumin after 24 weeks of treatment.

Secondary safety endpoints include:

- Pre-dialysis serum albumin measured on the first day of treatment and after every 4 weeks of treatment.
- Pre-dialysis Factor VII (MW = 50 kDa), Protein C (MW = 53-62 kDa) and Factor II (MW = 72 kDa) measured on the first day of treatment, after 4 weeks and after 24 weeks of treatment.
- Pre-dialysis Vitamin A measured on the first day of treatment, after 4 weeks and after 24 weeks of treatment.
- nPNA(nPCR) [normalized Protein equivalent of Nitrogen Appearance (normalized Protein Catabolic Rate)] calculated after every 4 weeks of treatment.
- Change from baseline to final measure in chemistry and hematology laboratory tests.
- Monitoring of adverse events (AEs), serious adverse events (SAEs) and Product Complaints (PCs) for Baxter related devices.

Statistical Methods:
Determination of Sample Size:

The sample size for this study is driven by the primary safety endpoint. The sample size calculation was performed using PASS procedure Non-inferiority Tests for the Difference Between Two Means. The power is based on a t-test with one-sided alpha level of 0.025 where the true difference in means is assumed to be zero (0) and the non-inferiority margin is 5%.

Pre-dialysis serum albumin was not evaluated in the previous Theranova 400 dialyzer HD study, only the mass (G) of albumin in the dialysate was assessed. However, a study published in PLoS ONE did use a prototype of the Theranova dialyzer (MCO-CI) where in pre-dialysis albumin levels were collected after a month of therapy and, based on these data, a mean and standard deviation (SD) of 35.3 and 3.7 was observed. Comparable pre-dialysis albumin levels are expected with body study dialyzers and with sample size of 70 patients per group, a t-test with 0.025 one-sided significance level will have 80% power to demonstrate non-inferiority of the Theranova 400 dialyzer compared to the Elisio-17H dialyzer as assessed by pre-dialysis serum albumin with a non-inferiority margin of 5%. To allow for 15% of patients to drop out, a total of 166 patients will be randomized 1:1 to treatment with the Theranova 400 dialyzer or treatment with the Elisio-17H dialyzer (i.e. 83 patients per group).

The 5% non-inferiority margin is based on results from 2 observational studies. These studies looked at the association between serum albumin levels and mortality in large US cohorts of HD and PD patients, respectively. In both, variations in serum albumin of +/- 1 g/L over 6 months (corresponds to +/- 0.1 g/dL) have been defined as “stable serum albumin levels”. A variation of +/- 1 g/dL is a range with a width of 2 g/L, which is larger than 5% if applied to the reported mean baseline serum albumin levels. Therefore, a 5% variation in serum albumin can be justified as having no clinical significance.

A previously conducted Theranova 400 dialyzer prototype HDF study was used to obtain λ FLC reduction ratio mean and standard deviation (SD) of 37.8 and 8.26. With a total sample size of 140 evaluable subjects as determined based on the primary safety endpoint (70 in the Theranova 400 dialyzer treatment group and 70 in the Elisio-17H dialyzer treatment group), a difference of 4.56 in the λ FLC reduction ratio in favor of the Theranova 400 dialyzer can be detected with 90% power at a two-sided 0.05 significance level using a two-sided two-sample t-test assuming equal variances. *Analysis Populations:*

The Per-protocol (PP) set will include all randomized patients who have received at least three months

treatment with a study dialyzer and do not have any major protocol violations that might impact the primary analysis.

The intent-to-treat full analysis (FA) set will include all randomized.

The primary analyses will be performed on the FA set and supported by an analysis using the PP set. All other analyses will be performed on the FA set unless otherwise noted.

Primary Safety Endpoint:

For the primary safety endpoint of pre-dialysis serum albumin after 24 weeks of treatment, let μ_T denote the Theranova dialyzer pre-dialysis serum albumin mean and let μ_R denote the Elisio-17H dialyzer pre-dialysis serum albumin mean. Then the null hypothesis to demonstrate non-inferiority using a 5% margin can be expressed as

Ho: $\mu_T - \mu_R \leq -1.765$. The alternative hypothesis is expressed as Ha $\mu_T - \mu_R > -1.765$.

An ANCOVA model with fixed effects of treatment and site and the continuous fixed covariate of baseline pre-dialysis serum albumin will be used to generate a two-sided 95% confidence interval (CI) for the difference in treatment means ($\mu_T - \mu_R$). If the lower bound is > -1.765 then non-inferiority will be demonstrated.

Primary Efficacy Endpoint:

For the primary efficacy endpoint of RR of λ FLC after 24 weeks of treatment, let μ_T denote the Theranova dialyzer RR of λ FLC mean at 24 weeks and let μ_R denote the Elisio-17H dialyzer RR of λ FLC mean at 24 weeks.

The primary safety analysis will be conducted first. If the primary safety analysis demonstrates non-inferiority, an ANCOVA model with fixed effects of treatment and site will be used to generate a two-sided 95% CI for the difference in treatment means ($\mu_T - \mu_R$). If the lower bound is > 0 then superiority will be demonstrated. The statistical testing of the primary efficacy endpoint of the reduction ratio (RR) of λ FLC after 24 weeks of treatment is contingent upon the outcome of the analysis of the primary safety endpoint and will only be conducted once non-inferiority could be established for the primary safety endpoint. This hierarchical testing approach guarantees that the overall type 1 error is controlled at a two-sided 0.05 significance level.

Secondary Safety Endpoint(s):

Pre-dialysis serum albumin:
A Mixed-effect Model Repeated Measurement (MMRM) model will be used to evaluate differences between treatment groups in the change from baseline in pre-dialysis serum albumin after each four weeks of treatment. The model will include the fixed effect of treatment, visit; the continuous, fixed covariate of baseline measurement; and the random effect of patient.

Pre-dialysis serum albumin will be further categorized at baseline and final measurement into 4 categories: <3.5, ≥3.5-3.9, ≥4.0-4.4, ≥4.5. Shift tables will be generated to cross tabulate the number of patients within each category by treatment.

Pre-dialysis Factor VII, Protein C, Vitamin A, and Factor II:
An MMRM model will be used to evaluate the differences between treatment groups in the change from baseline in pre-dialysis Factor VII, Protein C, Vitamin A, and Factor II after 4 weeks and after 24 weeks of treatment. The model will include the fixed effect of treatment, visit the continuous, fixed covariate of baseline measurement; and the random effect of patient.

nPNA (nPCR):
An MMRM model will be used to evaluate differences between treatment groups in nPNA (nPCR) collected after each 4 weeks of treatment. The model will include the fixed effect of treatment, visit, and the random effect of patient.

AEs, SAEs, and Product Complaints:
The summary of AEs will include AEs that occur on the day of or after the first study treatment. Adverse events will be mapped to a Primary System Organ Class (SOC) and Preferred Term (PT) according to MedDRA and summarized descriptively by SOC, PT and treatment group. Treatment group comparability in the incidence rates of adverse events will be evaluated using Fisher's exact test.

An overview (overall) summary table of all AEs will be generated that includes the total number of AEs, number and percentage of patient with at least one AE, number and percentage of patients with at least one SAE, number and percentage of patients with at least one severe AE, number and percentage of patients with at least one AE probably associated with study treatment, number and percentage of patients with an AE leading to study discontinuation and, number and percentage of patients with an AE leading to death. This summary table will be presented by treatment group and combining both groups (Total).

Furthermore, separate AE summary tables will be provided by SOC and PT for SAEs and AEs leading to study withdrawal. Separate AE summary tables will be provided to show a breakdown of AEs by SOC, PT and

a. Severity (mild, moderate or severe)

b. Relationship to study treatment (probably related, possibly related, unable to determine, unlikely related or not related).

Study dialyzer related product complaints will be summarized descriptively by study dialyzer.

Chemistry and hematology:
Mean differences between treatment groups in the change from baseline to final measure in chemistry and hematology laboratory tests will be analyzed using an ANCOVA with a fixed effect of treatment and a fixed continuous covariate of baseline laboratory value.

Secondary Efficacy Endpoint:

In order to account for multiplicity, secondary efficacy analyses will be held to a hierarchical assessment and performed in the order outlined below. If the first analysis results in a p-value <0.05, then formal testing will continue to the second analysis. If the second analysis also results in a p-value of <0.05, then formal testing will continue to the third analysis, and so on. This method of hierarchical assessment will continue until an analysis results in a p-value >0.05, i.e., is considered statistically insignificant. This hierarchical approach guarantees that the overall alpha will not exceed 0.05.

1. MMRM of RR of λ FLC
2. MMRM of RR of CFD
3. MMRM of RR of κ FLC
4. MMRM of RR of IL-6
5. MMRM of RR of TNFα
6. MMRM of RR of β_2-microglobulin
7. Change in pre-dialysis β_2-microglobulin from baseline to 24 weeks
8. MMRM of Kt/V_{urea}

An MMRM model will be used to evaluate differences between treatment groups in the reduction ratios of λ FLC, CFD, κ FLC, IL-6, TNFα, and β_2-microglobulin after 4 weeks and after 24 weeks of treatment. The model will include the fixed effect of treatment, visit, and the random effect of patient.

An ANCOVA with a fixed effect of treatment and a fixed continuous effect of baseline pre-dialysis β_2-microglobulin will be used to evaluate differences between treatment groups for the change from baseline in pre-dialysis β_2-microglobulin after 24 weeks of treatment.

An MMRM model will be used to evaluate differences between treatment groups in Kt/V_{urea} collected after each 4 weeks of treatment. The model will include the fixed effect of treatment, visit, and the random effect of patient.

Exploratory Endpoints:

An MMRM model will be used to evaluate differences between treatment groups in the change from

baseline in pre-dialysis serum levels of High sensitivity C-reactive Protein (hs-CRP) after each 4 weeks of treatment. The model will include the fixed effect of treatment, visit, as well as the continuous, fixed covariate of baseline measurement and the random effect of patient.

An MMRM model will be used to evaluate differences between treatment groups in the change from first day of treatment in KDQOL-36 and EQ-5D-5L after 12 weeks and after 24 weeks of treatment. The model will include the fixed effect of treatment, visit, as well as the continuous, fixed covariate of screening measurement and the random effect of patient.

Appropriate models will be used to evaluate differences between treatment groups in the utilization for medications (i.e., Erythropoiesis-stimulating agent (ESA), anti-hypertensives, iron).

Interim Analysis:

An interim analysis will be conducted when 60% of enrollment is completed. The purpose of the interim analysis is a blinded sample size reassessment using the approach by Friede and Kieser for an absolute difference in means which is based on the observed one-sample standard deviation calculated from the pooled data across treatment groups. This blinded sample size reassessment will be carried out by an independent statistician (who otherwise is not involved in the study conduct) using the 8 week measurements of the pre-dialysis serum albumin levels after 100 total patients have been enrolled (assuming 15% drop out, this corresponds to 84 evaluable patients). In case the observed pooled standard deviation at 8 weeks is larger than the assumed standard deviation of 3.7, the method will require an increase in overall sample size in order to maintain an overall power of 80%. If the observed standard deviation is smaller than the assumed standard deviation of 3.7, the overall sample size will be kept at 166.

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Date of Most Recent Protocol Amendment: 2018 FEB 09

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADE	Adverse Device Effect
AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CFD	Complement Factor D
CFR	Code of Federal Regulations
CI	Confidence Interval
CO_2	Carbon Dioxide
COV	Coefficient of Variation
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D-5L	EuroQol Five Dimensions Questionnaire
ESA	Erythropoiesis-Stimulating Agent
ESRD	End Stage Renal Disease
FA	Full Analysis
FDA	Food and Drug Administration
FLC	Free Light Chains
GCP	Good Clinical Practice
HD	Hemodialysis
HDF	Hemodiafiltration
HIPAA	Health Information Portability and Accountability Act
hs-CRP	High-sensitivity C-Reactive Protein
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IL-6	Interleukin 6
IRB	Institutional Review Board
ISO	International Organization for Standardization
KDQOL-36	Kidney Disease Quality of Life Questionnaire
Kt/V_{urea}	Dimensionless number used to quantify hemodialysis and peritoneal dialysis adequacy
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	Mixed-effect Model Repeated Measurement
MW	Molecular Weight
nPCR	normalized Protein Catabolic Rate
nPNA	normalized Protein equivalent of Nitrogen Appearance
PC	Product Complaint
PD	Peritoneal Dialysis
PI	Principal Investigator
PP	Per-Protocol
PRO	Patient Reported Outcome
PT	Preferred Term
PUR	Polyurethane
Q_B	Blood Flow Rate
Q_D	Dialysate Flow Rate
RCT	Randomized Controlled Trial
RR	Reduction Ratio
RRT	Renal Replacement Therapy
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
SOC	System Organ Class
SOP	Standard Operating Procedure
TNFα	Tumor Necrosis Factor Alpha
USA	United States of America
β-hCG	Beta Human Chorionic Gonadotropin

1. INTRODUCTION

1.1 Background and Rationale

The incidence and prevalence of chronic kidney disease are increasing worldwide, as is the number of patients progressing to end stage renal disease (ESRD). The number of patients with ESRD has been increasing by 5% to 8% per annum in higher-income countries, and by the same rate or more in lower-income countries.[1-5] The incidence rate of treated ESRD in the United States of America (USA) was 370 per million population/year for 2014, and the prevalence of treated ESRD patients was 2076 per million population for 2014. In the USA alone, there was a 1.1% increase in new ESRD cases and 3.8% increase of patients treated for ESRD from 2013 to 2014.[6] Understanding these trends is important in evaluating and predicting the global impact of ESRD on public health.

Without renal replacement therapy (RRT), either in the form of maintenance dialysis or transplantation, ESRD is fatal. Given the limited supply of donor kidneys, dialysis remains the mainstay treatment for patients with ESRD. Although dialysis is more commonly used in ESRD patients requiring chronic RRT (> 30 days), it can also be used in clinical settings of acute kidney injury. Dialysis may be prescribed when less than 10% of kidney function remains available. Dialysis may be started even earlier in patients with serious complications, such as volume overload (usually secondary to acute heart failure), hyperkalemia, metabolic acidosis, or if renal failure cannot be controlled by medication.

Patients undergoing hemodialysis (HD) therapy receive treatments intermittently for a specific number of hours per session and a specific number of sessions per week. All extracorporeal dialytic therapies require the removal of blood from the patient's circulatory system and the circulation of this blood through a circuit. This circuit contains a semi-permeable membrane within a dialyzer device to remove nitrogenous end-products of catabolism and begin the correction of the salt, water and acid-base derangements associated with renal failure. As dialysis treatment requires access to the blood circulation, a vascular access is required, which can be in the form of a fistula, graft or a HD catheter.

The molecular weight (MW) range of uremic toxins, including β_2-microglobulin, free light chains (FLCs), cytokines and other inflammatory mediators, is about 10 to 50 kDa. There is a growing body of evidence that large uremic solutes in the range of 20 to 50 kDa play a significant role in clinical complications in dialysis patients.[7-10] Recent reviews on uremic toxicity indicate that an abundance of middle molecules accumulate in serum leading to uremia; many uremic toxins are in a size above 15 kDa.[11] Other

investigators have shown that some of those proteins, particularly isoforms containing post-translational modifications induced by the uremic environment, qualify as uremic toxins. Emerging evidence based on new methodology suggests that some of the morbidity associated with uremia is the result of the collective retention of many such modified proteins, suggesting a role for dialytic strategies aimed at their collective removal.

While conventional high-flux membranes are designed to remove β_2-microglobulin effectively, the removal of larger middle molecules is substantially less effective when such membranes are used in HD[12] due to the rapid fall-off in diffusive clearance with increasing molecular size.[13] Hemodiafiltration (HDF) is a therapy designed to increase convective solute removal when conventional high-flux membranes are used, with a special focus on middle molecule uremic solutes.[14] Hemodiafiltration is increasingly practiced in Europe, and many other parts of the world outside USA, recently estimated to account for approximately 27% of hemodialysis treatments in Europe.[15] Although an HDF system has been approved for use in USA (K112314, April 2012), its use in USA is negligible.

Hemodiafiltration has shown to offer outcome benefits in large randomized controlled trials (RCTs). However, special equipment and large volumes of replacement fluid are needed to deliver HDF at a treatment dose for which outcome benefits have been demonstrated in RCTs. With the Theranova dialyzer, a middle molecule clearance equivalent to HDF therapy can be obtained without the need to use the more complex equipment and high volumes of replacement fluid. Replacement fluid is used in HDF therapy as it addresses middle sized uremic solutes, while sparing larger sized molecules such as albumin.

1.2 Benefits and Risks for the Study Population

The risks and benefits of hemodialysis are well characterized. The same risks and benefits will apply to patients undergoing dialysis with Theranova dialyzers. During dialysis, toxins and beneficial molecules can be removed. Theranova dialyzers can remove a larger size range of molecules, therefore patients may see greater removal of "middle molecules", including coagulation factors. Studying these molecules *in vivo* is expected to complement previous *in vitro* investigations on single (simulated) treatment removal of coagulation factors by providing longer term data.

Studies of therapies that remove middle molecules more effectively than HD with typical high permeability dialyzers do not suggest that there is an increased risk from removing solutes of this size, and indicate that there may be benefits to removal of the uremic

toxins. The recent progress in dialysis treatment may improve the removal of these toxins and though there is insufficient evidence on reducing mortality there may be benefits on patient outcomes.[12]

Although the Theranova dialyzer is known to remove more albumin per treatment than high-flux dialyzers, the albumin sieving of the membrane is <1%, which is below what is given by Ward as definition of protein-leaking membranes (1-3%). The average clinical albumin loss of 3 g per 4 h hemodialysis session[16] is also at the lower end of his definition (2-6 g/4 h). Increased patient mortality is correlated with low serum albumin levels, but not directly correlated with albumin loss per treatment. Human serum albumin homeostasis in general and in various disease states[17], particularly in patients on dialysis, has been extensively reviewed. Although observational studies have shown a significant association between lower serum albumin level and greater risk of all-cause death, in HD patients as well as in peritoneal dialysis (PD) patients recent research has led to the conclusion that the association between serum albumin and outcome is principally mediated by inflammation and that, at least in renal failure patients, there is evidence that plasma concentration is determined primarily by the rate of liver albumin synthesis, and this synthesis is decreased in inflammatory states. Albumin is a negative acute phase reactant and uremic inflammation, which is common in dialysis patients, is a main determinant of a low serum albumin level through reduced synthesis of albumin.[18,19] Inflammation is in itself a significant and powerful risk factor for poor outcome in dialysis patients.[20]

1.3 Study Sponsor

Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, IL 60015 USA

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary efficacy objective of this study is to demonstrate that the Theranova 400 dialyzer has performance superiority to the Elisio-17H dialyzer in removing lambda immunoglobulin free light chains (λ FLCs).

The primary safety objective of this study is to demonstrate that performance of the Theranova 400 dialyzer compared to the Elisio-17H dialyzer is non-inferior, in regards to maintaining pre-dialysis serum albumin.

2.2 Secondary Objective(s)

The secondary objectives of this study are to evaluate the performance of the Theranova 400 dialyzer compared to the Elisio-17H dialyzer in removing serum middle molecules, dialysis adequacy, levels of coagulation factors, and characterize monthly trends in pre-dialysis serum albumin levels.

2.3 Exploratory Objectives

The exploratory objectives for this study include:

- Evaluation of patient reported quality-of-life assessments.
- Evaluation of serum levels of the inflammatory marker high sensitivity C-Reactive Protein.

3. INVESTIGATIONAL PLAN

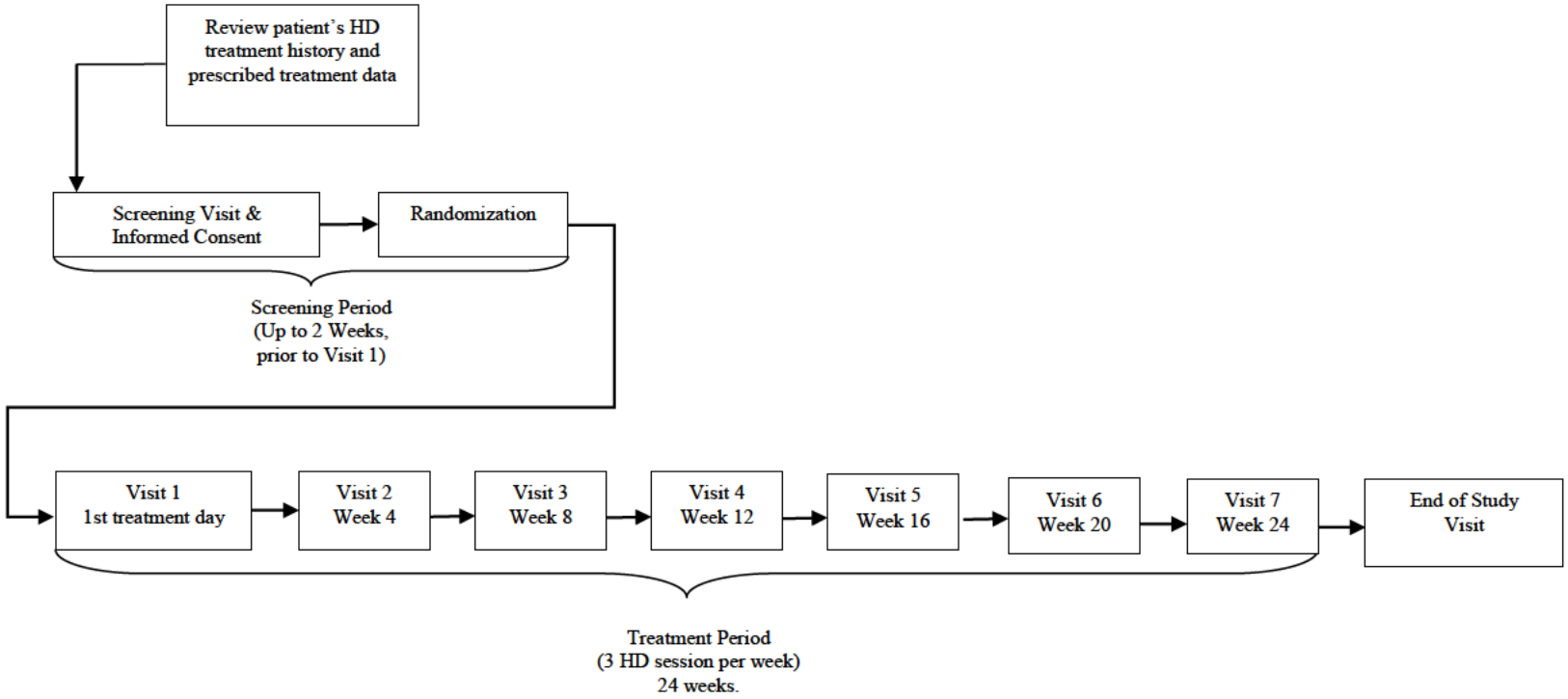
3.1 Overall Study Design and Plan

This is a multi-center, prospective, randomized, controlled, open-label, parallel study to evaluate medically stable ESRD patients receiving dialysis treatment with either the Theranova 400 dialyzer or the Elisio-17H dialyzer for 3 sessions weekly, over 24 weeks.

A sufficient number of patients will be enrolled in the study in order to randomize 166 patients in a 1:1 manner to either the Theranova 400 dialyzer or the Elisio-17H dialyzer. The study will be conducted in up to 30 study centers in the USA.

The study will have an overall duration of approximately 27 weeks per patient. This period will consist of up to 2 weeks screening period, followed by a first treatment day visit and consequent3 dialysis sessions per week in an in-center setting over a 24 week period, at the end of the study there will be a visit occurring on the next HD session. The assessments performed, on a monthly basis, are shown in the Schedules of Evaluation in Appendix 1 and Appendix 2. Patients will initiate their HD treatment on their randomized study dialyzer, either Theranova 400 dialyzer or Elisio-17H dialyzer, at the midweek HD session (Wednesday or Thursday), and will then continue to have 3 dialysis sessions per week. During the treatment period, initial blood samples will be taken on the day of the first study dialyzer treatment and subsequent blood sampling samples will be taken after each 4 weeks of treatment, during the midweek HD session as illustrated in Appendix 1. A scheme for the study is shown in Figure 1 below. The overall duration of the complete study will be approximately 9 months to allow sufficient time for patient recruitment.

Figure 1. Trial Schematic[a]



[a] All study visits are performed during the mid-week treatment session.

3.2 Study Endpoints

3.2.1 Primary Endpoints

The primary efficacy endpoint is the Reduction Ratio (RR) of λ FLC after 24 weeks of treatment.

The primary safety endpoint is the pre-dialysis serum level of albumin after 24 weeks of treatment.

3.2.2 Secondary Endpoints

Secondary efficacy endpoints include:

- Reduction ratio of λ FLC measured on the first day of treatment and after 4 weeks of treatment.
- Reduction ratio of complement factor D (CFD; MW = 27 kDa), κ FLC (MW = 23 kDa), interleukin 6 (IL-6; MW = 25 kDa), tumor necrosis factor alpha (TNFα; MW = 51 kDa), and β_2-microglobulin (MW = 11.6 kDa) measured after 4 weeks and after 24 weeks of treatment.
- Change in pre-dialysis β_2-microglobulin measured on the first day of treatment and after 24 weeks of treatment.
- Kt/V_{urea} measured after every 4 weeks of treatment.

Secondary safety endpoints include:

- Pre-dialysis serum albumin measured on the first day of treatment and after every 4 weeks of treatment.
- Pre-dialysis Factor VII (MW = 50 kDa), Protein C (MW = 53-62 kDa) and Factor II (MW = 72 kDa) measured on the first day of treatment, after 4 weeks and after 24 weeks of treatment.
- Pre-dialysis Vitamin A measured on the first day of treatment, after 4 weeks and after 24 weeks of treatment.
- nPNA (nPCR) calculated after every 4 weeks of treatment.
- Change from baseline to final measure in chemistry and hematology laboratory tests (see Table 1).
- Monitoring of adverse events (AEs), serious adverse events (SAEs) and product complaints (PCs) for Baxter related devices.

3.2.3 Exploratory Assessments

Exploratory assessments include:

- Inflammatory marker high-sensitivity C-Reactive protein (hs-CRP) measured pre-dialysis on the first day of treatment and after every 4 weeks of treatment.
- KDQOL-36 measured on the first day of treatment, after 12 weeks and after 24 weeks of treatment.
- EQ-5D-5L measured on the first day of treatment, after 12 weeks and after 24 weeks of treatment.
- Changes in utilization for medication (i.e., erythropoiesis-stimulating agent (ESA), anti-hypertensives, iron).

3.3 Rationale for Study Design and Control Group

This multi-center, prospective, randomized, controlled, open-label, parallel study is designed to demonstrate superiority of the Theranova 400 dialyzer compared to the Elisio-17H dialyzer in regards to removal of λ FLCs and safety of the Theranova 400 dialyzer during extended use (study duration 24 weeks). The Elisio-17H dialyzer is a marketed, Food and Drug Administration (FDA) cleared hemodialyzer device with comparable design, membrane polymers and surface area, and performance specifications to the study device. The main difference between the Theranova 400 dialyzer and the Elisio-17H dialyzer is the larger pore size within the Theranova 400 dialyzer, which allows a wider range of molecules to diffuse across the device membrane without the need of convection.

Both devices will be studied in medically stable patients who require chronic hemodialysis therapy due to end stage renal disease. The dialysis prescriptions for the Theranova 400 dialyzer follow the same method as for a conventional high-flux dialyzer; no device-specific modifications to the dialysis prescriptions are required. Use of the study devices during the study treatment period is consistent with conventional, current institutional practice.[21]

Benefits of the Theranova dialyzer products are associated with the removal of serum middle molecules. The removal of serum middle molecules such as λ FLCs, may be associated with a reduction in both patient morbidity and mortality.[22-25] Data from this clinical study will also be used to support the new device classification for Theranova dialyzer, as a new device modality that effectively reduces serum levels of middle molecules such as λ FLCs during individual HD treatments.

As part of this evaluation, Baxter has chosen to study representative beneficial molecules in addition to uremic toxins. Baxter has selected three beneficial molecules to study. The pre-dialysis serum levels of the following molecules will be measured on the first day of treatment, after 4 and after 24 weeks of treatment:

1. Factor VII (Activates IX, X): 50,000 Da (bleeding diathesis)
2. Protein C: 53,000-62,000 Da (deficiency causes hypercoagulable state)
3. Factor II: 72,000 Da (deficiency causes bleeding disorder)

In addition, Vitamin A levels will be measured on the first day of treatment, after 4 weeks and after 24 weeks of treatment.

We have focused on coagulation factors because coagulation abnormalities such as hypercoagulability and thrombosis are common in patients with end stage renal disease on maintenance hemodialysis. The selected molecules have deficiencies that manifest phenotypically, are well described (Factor VII deficiency, Factor II deficiency, Protein C deficiency), and represent different parts of the coagulation cascade. They are too large to be effectively removed by high-flux hemodialysis only, but represent the higher end of the Theranova dialyzer removal range. Studying these molecules *in vivo* is also expected to complement previous *in vitro* investigations on single (simulated) treatment removal of coagulation factors by providing longer term data for potential changes in coagulation factors. Baxter believes that the comparison of the Theranova dialyzer cohort to the high-flux dialysis control group will examine the significance of changes in serum levels.

3.3.1 Other Considerations

The participating healthcare professionals must be familiar with the use of both Theranova 400 dialyzer and Elisio-17H dialyzer. All participating healthcare professionals will be trained on both types of dialyzers before the first patient is treated.

3.4 Study Duration and Dates

Patients will undergo 3 dialysis sessions per week, for 24 weeks. The participating patients should continue with their pre-study HD prescriptions (in terms of treatment time, blood flow rate and dialysate flow rate) and prescriptions should be kept stable throughout the study.

3.5 Study Discontinuation Rules

The study should be suspended if suspicion of an unacceptable risk to the patients arises during the clinical investigation, or when instructed by the Institutional Review Board

(IRB) or regulatory authorities. Risks to patients could be indicated when any of the following events occur:

- Device malfunction, considered by the investigators and/or Baxter Healthcare as possibly leading to a deficiency in the patient's treatment
- Repeated patient discomfort with the product
- Unexpected/Unanticipated Serious Adverse Device Effect (SADE)

The Sponsor shall review untoward events and assess risks during the conduct of the clinical investigation. Decision to restart the study will be made jointly by Baxter Healthcare and the coordinating investigator following evaluation of the problems encountered and implementation of mitigation steps. The Sponsor shall terminate the clinical investigation if an unacceptable risk is confirmed to be not mitigatable.

3.5.1 Procedure for Resuming the Clinical Investigation after Temporary Suspension

When the Sponsor concludes an analysis of the reasons(s) for the study suspension, implements the necessary corrective actions and decides to lift the temporary suspension, the Sponsor shall inform the principal investigators (PIs), the IRB, and where appropriate, the regulatory authority of the rationale and provide them with the relevant data supporting this decision.

Concurrence shall be obtained from the IRB and, where appropriate, regulatory authorities before the clinical investigation resumes.

If patients have been informed of the suspension, the PI or authorized designee shall inform them of the reasons for resumption.

4. STUDY POPULATION SELECTION

4.1 Study Population

The study population consists of subjects with ESRD who have been stable and receiving HD therapy at least 3 times a week for 3 months prior to enrollment. A sufficient number of patients will be enrolled in the study in order to randomize 166 patients in a 1:1 manner to either Theranova 400 dialyzer or the Elisio-17H dialyzer. The study will be conducted in up to 30 study centers in the USA.

4.2 Inclusion Criteria

All of the following criteria must be met for the patient to be enrolled in this study.

1. ESRD patients age 22 and older, or between ages 18 and 21 with a weight ≥ 40 kg.
2. Clinically stable as judged by the treating physician and as demonstrated by stable medical history for 30 days prior to enrollment, physical examination, and laboratory testing.
3. Hemodialysis therapy with high-flux dialyzers for at least 3 months immediately prior to study enrollment and expected to survive for the next 12 months.
4. Expected to maintain an acceptable urea clearance (Kt/V) with a dialyzer of an approximate surface area of 1.7 m^2.
5. Currently being dialyzed at an in-center setting, on a schedule of 3 times per week.
6. Able to give informed consent after an explanation of the proposed study, and who are willing to comply with the study requirements for therapy during the entire study treatment period.
7. Have a stable functioning vascular access (arteriovenous fistula, graft, or dual-lumen tunneled catheter); stable access will be confirmed by observed Kt/V ≥ 1.2 for past 2 measurements and/or achievement of within 15% the prescribed blood flow rate over 3 treatments prior to study entry.

4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study. This study will exclude subjects who:

1. Are female and pregnant, lactating, or planning to become pregnant during the study period. Note: Female subjects of childbearing potential, defined as women < 55 years old who has not had a partial or full hysterectomy or oophorectomy, must have a negative serum beta human chorionic gonadotropin (β-hCG) pregnancy test at screening. Subjects of childbearing potential must use a medically acceptable means of contraception during their participation in the study.
2. Have chronic liver disease.
3. Have a known paraprotein-associated disease.
4. Have known bleeding disorders (e.g., gastrointestinal bleed, colonic polyps, small bowel angiodysplasia, and active peptic ulcers).

5. Have had a major bleeding episode (i.e. soft tissue bleeding, blood in stool, prolonged nose bleeds, joint damage, retinal bleeding, extensive mucosal bleeding, exsanguination, cerebral hemorrhage) ≤ 12 weeks prior to randomization.
6. Have had a blood (red blood cell) transfusion ≤ 12 weeks prior to randomization.
7. Have had an acute infection ≤ 4 weeks prior to randomization.
8. Have active cancer, except for basal cell or squamous cell skin cancer.
9. Have a known serum κ/λ FLC ratio that is less than 0.37, or greater than 3.1.[b]
10. Have a known monoclonal gammopathy (monoclonal gammopathy of uncertain significance, smoldering [asymptomatic] multiple myeloma, symptomatic multiple myeloma, plasmacytomas, or plasma cell leukemia).
11. Have a known polyclonal gammopathy (connective tissue disease, liver disease, chronic infection, lymphoproliferative disorder, or other hematologic conditions).
12. Have a positive serology test for human immunodeficiency virus or hepatitis infection.
13. Have a significant psychiatric disorder or mental disability.
14. Are scheduled for planned interventions requiring hospitalization > 1 week.
15. Are scheduled for living-donor transplantation within the study period + 3 months, plan to change to PD therapy within the next 9 months, plan to change to a home hemodialysis treatment, or plan to relocate to an area where no study center is located.
16. Are currently participating in another interventional clinical study or has participated in another interventional clinical study in the past 3 months.
17. Have a history of non-compliance with HD as assessed by an investigator.
18. Have had a major cardiovascular or cerebrovascular event within 3 months of study entry.
19. Have a history with consistent evidence of intradialytic hypotension.
20. Have uncontrolled (systolic blood pressure (BP) > 180 mmHg) hypertension.
21. Have had adverse reactions to dialyzer materials.

[b] In patients with renal impairment 0.37 to 3.1 is the normal range for serum κ/λ FLC ratio.

4.4 Recruitment

Recruitment for the study will commence after review and approval from the IRB for each respective study center. After the patient has received the Informed Consent Form (ICF) and allowed time to consider their participation in the study, inclusion and exclusion criteria will be verified. Patients will be considered enrolled in the study once the ICF has been signed and inclusion/exclusion criteria have been confirmed.

4.5 Removal of Patients from Therapy, Assessment, or Study

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

1. AE
2. Inadequate dialysis based on Investigator judgement
3. Protocol violations (i.e. the patient fails to meet protocol entry criteria or does not adhere to protocol requirements)
4. Pregnancy
5. Lost to follow-up (i.e. patient fails to return for study visits)
6. Voluntary withdrawal (i.e. patient's request)
7. Termination of study
8. Investigator's discretion
9. Renal transplantation
10. Switch to PD
11. Death
12. Change to another dialysis center, that is not a clinical study site
13. Missing 3 consecutive study treatments
14. Other reason (with reason noted on the electronic case report form [eCRF])

The Investigator may terminate a patient's study participation at any time during the study if he/she judges it to be in the patient's best interest. In addition, a patient may discontinue his or her participation any time during the study without having to justify his/her decision. If a patient's participation is discontinued, the reason(s) must be recorded in the source documents and on the eCRF. If a patient discontinues for any reason, every effort should be made to perform all of the procedures that are scheduled

for the follow-up visit occurring at the pre-dialysis on the next treatment day. In addition, SAEs (related or not) and adverse device effects (ADEs), will be followed until resolution or stable, including following the patient after the end of the study if necessary. The Investigator or designee should inform their site monitor the moment any patient is withdrawn or discontinued from the study, regardless of the reason(s) for withdrawal or discontinuation.

4.6 Missed Visits

In general, missed dialysis session visits will not be replaced. If a patient misses a mid-week dialysis session, where a study treatment visit was scheduled to occur, the missed study visit procedures will be performed during the next mid-week dialysis session and subsequent visits and follow-up visit will occur as planned. However, if the patient fails to return for that mid-week dialysis session and also misses the subsequent week (a third mid-week session), then the patient will be terminated from the study. Study termination also applies if the patient misses 3 consecutive study treatments (i.e. missing a full week of dialysis). Reasons for missed visits will be captured on the eCRF.

5. STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Study Device – Theranova 400 dialyzer

Theranova dialyzers are indicated for treatment of chronic and acute renal failure by dialysis. This study is intended to support an indication for extended hemodialysis to remove middle molecular uremic toxins.

The membrane used in Theranova 400 dialyzer is a blend of polyarylethersulfone and polyvinylpyrrolidone. Each hollow fiber has an inner diameter of approximately 180 µm and a wall thickness of approximately 35 µm, the effective membrane length is 236 mm, with an effective surface area of 1.7 m^2. On each end of the device the hollow fibers are potted in polyurethane (PUR) to isolate the blood compartment from the filtrate dialysate compartment. The housing and the end caps of the dialyzer are made of polycarbonate. Dialysis fluid and blood connectors are designed according to ISO 8637. Theranova 400 dialyzer is sterilized by steam, according to ISO 17665-1.

5.1.2 Study Device – Elisio-17H dialyzer

The membrane used in the Elisio-17H dialyzer (Polynephron™) is made of Polyethersulfone and Polyvinylpyrrolidone. The fiber walls are 40 µm thick, and have an internal diameter of about 200 µm. The effective length is 271 mm, with an effective surface area of 1.7 m^2. On each end of the device the hollow fibers are potted in PUR to

isolate the blood compartment from the filtrate dialysate compartment. The housing and the end caps of the dialyzer are made of Polypropylene. The Elisio-17H dialyzer is sterilized by dry gamma irradiation.

Hemodialysis with an Elisio-17H hemodialyzer is indicated for patients with acute or chronic renal failure when conservative therapy is judged to be inadequate. It may also be indicated in the treatment of patients intoxicated with poisons or drugs. It is FDA cleared under 510(k) K131935.

5.2 Treatments Administered

All randomized patients will receive dialysis treatments with either Theranova 400 dialyzer or Elisio-17H dialyzer, 3 times weekly for a period of 24 weeks. Trained HD staff will administer all treatments.

5.3 Selection and Timing for Each Patient

Treatments will occur at sites that routinely implement high-flux dialysis. Dialysis prescription and management will be performed per institutional practice. All patients will receive in-center HD treatments, 3 times per week for a total of 24 weeks using the study device which he/she has been randomized to. Actual treatment duration of the individual dialysis session will vary based on clinical requirements determined by the treating physician.

Hemodialysis treatment duration per session for each individual patient will vary based on clinical requirements determined by the Investigator, based on the patient's need, residual renal function (via estimated Glomerular Filtrations Rate), access function, tolerance to HD and other relevant factors. The participating patients' HD prescriptions should be kept stable throughout the study; any changes to the prescriptions must be recorded.

5.4 Method of Assigning Patients to Treatment Groups

All patients who sign the ICF will be assigned a unique patient identification number. Only patients confirmed to meet screening eligibility will be randomized and allowed to continue in the study. A sufficient number of patients will be enrolled in the study in order to randomize 166 patients across up to 30 study sites.

The type of study dialyzer each patient will use during their treatment sessions will be determined according to a central randomization scheme provided by Baxter (via the Electronic Data Capture [EDC] system used for the study). Patients will be randomly assigned to receive one of the following two study dialyzers in a 1:1 ratio:

- Theranova 400 dialyzer
- Elisio-17H dialyzer

Randomization will be stratified by site and dynamic allocation will be used.

5.5 Blinding

This is an open-label study and will not have blinding of any investigational products. However, the Medical Monitor, Study Statistician, Data Management and the central laboratory will be blinded to treatment as a means to minimize potential bias. A non-blinded statistician will be assigned to this study.

5.6 Concomitant Therapy

The PI should review any additions or changes in concomitant therapy. All medications should be recorded in the source documents or equivalent. Prior medications, defined as all medications at screening and any ESA taken in the last 30 days before the study begins (ICF), will be recorded on the eCRF. Concomitant medications, including dose, unit, frequency, route of administration, start and stop dates and indication for use, will be recorded on the eCRF throughout the study. Sites will not enter "other" or "prophylaxis" as indications.

Erythropoiesis-stimulating agents are often used to stimulate red blood cell production in dialysis patients. During the course of this study, ESAs should be administered according to each clinic's standard practices, either subcutaneously or intravenously. If administered intravenously, it should be done post-dialysis or in the venous part of the extracorporeal circuit (downstream of the dialyzer).

A treatment medication will be anything given once the patient enters Visit 1.

5.7 Prohibitions and Restrictions

Sites must demonstrate they have monthly microbiological water/dialysate quality testing done according to current Centers for Medicare and Medicaid Services regulations for dialysis water (ANSI/AAMI RD62:2001) and conventional dialysate (ANSI/AAMI RD52). Sites will also adhere to all requirements stipulated by their respective IRB.

There are no activity or diet restrictions specific to the study. Patients should discuss their daily diet and activities with their physician. Medical management of HD patients is per institutional practice. Dialysis prescription and management will be per institutional practice.

5.8 Treatment Compliance

Each patient should receive 73 treatments during the 24 week study period. Treatment compliance will be assessed by counting the number of scheduled treatments delivered to each patient within the study period. A patient may be withdrawn from the study if more than 3 consecutive treatments with the randomized dialyzer/treatment mode are missed.

5.9 Packaging and Labeling

The investigational product, Theranova 400 dialyzer, will be provided by the sponsor in sterilized individual peel pouches. All other products used in the management and care of patients in the trial will be provided by the site. Each dialyzer will be labeled, at a contract research organization approved facility, with a unique number for product accountability.

Each Theranova 400 dialyzer overpouch will be labeled per Title 21 of the Code of Federal Regulations (CFR) Part 812.5 and Part 801.1.

All Theranova dialyzers in the USA will minimally include the investigational statement on the peel pouch:
"Caution – Investigational Device. Limited by Federal (or United States) law to investigational use."

5.10 Storage and Accountability

The Theranova 400 dialyzers will be imported from Germany to a clinical locker in the USA. The investigators at each site will then be supplied with the investigational product for this clinical study. Baxter will sponsor the cost associated with ordering the Elisio-17H dialyzers; these dialyzers will be stored at a Clinical locker and/or at the study site. The person in charge of receiving the products at site must initiate the accountability documentation process. The recording method defined and approved during the "study initiation visit" shall apply and the required documents ("Good Clinical Practice [GCP] forms") shall be filled out as needed, and when required.

The Theranova 400 dialyzers must be stored below +30°C and the Elisio-17H dialyzers must be stored per label claims, in a safe space, with restricted access and only used to treat patients included in the study.

The Investigator will ensure study devices are tracked by unique identifier and maintain adequate records of the disposition of the study devices. The following requirements must be noted:

1. The date of receipt at the study site
2. Identification of each study device (unique identification assigned by clinical locker)
3. The date of use
4. Patient identification
5. The date of return of unused, expired or malfunctioning study devices, if applicable.

Prior to initiating treatment the study monitor must ensure that the investigator has sufficient number of products (or material) at his/her disposition, that products have been duly counted and that the products are being used correctly, according to their intended use as labeled.

All investigational devices will be provided, reconciled and accounted for throughout the study. Periodically throughout the study, the site monitor will collect copies of accountability documentation. In addition at the conclusion of the study, copies of accountability records will be collected showing investigational product delivery, inventory, dispensation, return and disposition from the clinical locker, investigational site and study patients.

All unused study devices at investigational sites will be returned to the Sponsor/designee. If needed, the Sponsor may authorize an alternative disposition of unused products. However, disposition can only occur after the Sponsor has been notified and given written authorization. The Sponsor will maintain a written record of any authorized disposition of the investigational products.

All used disposable products at investigational sites must be disposed of per site standard operating procedures (SOPs).

6. STUDY PROCEDURES

6.1 Informed Consent

Prior to collecting any study data, written patient informed consent must be obtained in accordance with 21 CFR Part 50. The Investigators must ensure that the patients have received all relevant information, orally and in writing, relating to the type, objective and possible risks and benefits of the study. Patients must also be informed that they are free to withdraw from the study at any time. The information will be given in reasonable time before study start. The informed consent statement will be reviewed, signed and dated by the patient and the person who administered the informed consent. A copy of the signed

ICF will be given to the patient and the original will be placed in the patient's medical record. Confirmation of a patient's informed consent must also be documented in the patient's medical records prior to any data collection under this protocol. An IRB approved patient ICF will be provided to the Investigator. The ICF must not be altered without the prior agreement of the relevant IRB and Baxter.

If modifications are needed according to local regulations, or if new information becomes available (e.g., from Baxter) that can significantly affect a patient's future health and medical care, a new version of the patient information and informed consent form must be prepared in cooperation with the investigator(s) and approved by Baxter. Patients still participating in the study must provide written informed consent by signing the updated consent form and will receive a copy of the signed form and the patient information. A copy of the new version of the form and patient information shall be given to each previously enrolled patient for information.

Upon signature of the ICF, the study patient will be screened to verify eligibility (see Inclusion and Exclusion Criteria in Sections 4.2 and 4.3, respectively).

6.2 Demographics and Baseline Characteristics

Demographics will include the date of birth, gender, and ethnicity.

A complete medical history including a review of all major body systems and medical history, as applicable, will be performed.

Information regarding the type and frequency of dialysis therapy received prior to enrollment in this study, and the type of access will be obtained. The information gathered will include mean duration of treatments, blood flow rate (Q_B), dialysate flow rate (Q_D) and the type and mean dosage of heparin, erythropoietin and intravenous iron administered.

Relevant medical history for each patient will be obtained during Screening. Medication history, if applicable, will also be evaluated during the Screening period. Past and present conditions, as well as surgical procedures, will be recorded for the main body systems.

Renal medical history, date and type of first chronic dialysis treatment, date of last transplant (if applicable), date of last transplant failure (HD resumed, if applicable), primary renal disease etiology will also be captured in the eCRF. In addition, all medications being taken at Screening and any ESA taken in the 30 days before Screening will be recorded.

6.3 Physical Examination

Physical examinations will be performed during Screening and at the End of Study visit which will be conducted after the patient's last study treatment. During the study, any new condition or worsening of a pre-existing condition from the time a patient signs the ICF will be noted and recorded on the AE eCRF page. Height will be measured at screening only.

A complete physical exam will be performed; edema status, height (at Screening) and body weight will be recorded. Weight will be measured at Screening and at the end of study visit.

A final physical examination will be performed on patients who complete Screening, enter the study, but discontinue from the study early.

6.4 Vital Signs

Vital signs will be assessed at screening, during treatment period visits and at the end of study visit. Vital signs will include measurements of sitting blood pressure, sitting respiratory rate, temperature and sitting pulse rate. Blood pressure will be measured with an appropriate cuff size after the patient has been sitting for 5 minutes. Any new condition or worsening of a pre-existing condition from signing of the ICF will be noted and recorded on the AE eCRF.

6.5 Clinical Laboratory Tests

6.5.1 Laboratory Parameters

Laboratory tests will include tests for hematology and serum chemistry as listed in Table 1. These tests will be carried as per schedule in Appendix 2.

The Investigator will receive the laboratory results directly from the central laboratory for review and signature. The Investigator will be notified of any laboratory value that is outside of the normal range, as defined by the laboratory. If a clinically significant change from Screening or the previous visit occurs for any laboratory value and results in medical intervention, as judged by the Investigator, the laboratory abnormality will be recorded as an AE on the eCRF. The Clinical Laboratory Evaluations eCRF page will capture and reconcile with the electronic laboratory data transfer, the sample date and time, test accession number, and if the test is an initial or re-test.

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include the following:

Table 1. List of Laboratory Tests

Hematology:

- Hematocrit
- Hemoglobin
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Platelet count
- Red blood cell count
- White blood cell count with differential

Coagulation:

- Prothrombin time
- INR
- Activated partial thromboplastin time

- λ FLC
- κ FLC
- TNFα
- IL-6
- β_2-microglobulin
- CFD
- Vitamin A
- Factor VII
- Protein C
- Factor II
- hs-CRP
- Hepatitis A, B and C
- Human Immunodeficiency Virus
- β-hCG (if applicable)

Serum Chemistry:

- Albumin
- Alkaline phosphatase
- ALT; SGPT
- AST; SGOT
- BUN
- Calcium
- Bicarbonate
- Chloride
- Creatinine
- Gamma-glutamyl transferase
- Globulin
- Glucose
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Direct bilirubin
- Total protein
- Total cholesterol
- HDL cholesterol
- LDL cholesterol
- Triglycerides

Note: λ FLC – Lambda Free light chains, κ FLC – Kappa Free light chains, TNFα – Tumor necrosis factor alpha, IL-6 – Interleukin 6, CFD – Complement factor D, hs-CRP – high-sensitivity C-reactive Protein, β-hCG – Beta human chorionic gonadotropin, ALT;SGPT – Alanine aminotransferase; Serum glutamic pyruvic transaminase, AST;SGOT – Aspartate aminotransferase; Serum glutamic oxaloacetic transaminase, BUN – Blood urea nitrogen, HDL – High-density lipoprotein, LDL – Low-density lipoprotein

6.5.2 Sample Collection, Storage, and Shipping

All blood samples, as part of the collection of dialysis treatment data, will be collected by the sites and stored, shipped and processed according to the central laboratory requirements and procedures. Methods, units and ranges for those parameters shall be made available to the Sponsor before the start of the study.

Patients will be in a seated or supine position during blood collection. No puncture of the patient is necessary, as the blood samples will be taken from the fistula needle or from the sampling port of the blood line.

6.6 Patient Reported Outcomes

Patients will be asked to complete 2 surveys as part of the exploratory assessments. These patient reported outcomes (PROs) surveys are KDQOL-36 and EQ-5D-5L.

These questionnaires will be completed independently and this will be done on ePRO devices. Study sites will be instructed to ensure that the study subjects complete the questionnaires.

6.7 Appropriateness of Measurements

Measurements for the primary and secondary endpoints have been aligned with FDA for the purposes of a future pre-market submission. Hematology and other chemistry measurements used to evaluate safety are standard for the indication or patient population being studied.

7. DATA COLLECTION FOR SAFETY ASSESSMENTS AND REPORTING

7.1 Definition of Adverse Events and Product Complaints

Table 2. Adverse Event Term Definition

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or on toward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the medical device. This includes events related to the investigational device or the comparator. This includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional

Table 2. Adverse Event Term Definition

Term	Definition
	misuse of the investigational medical device. (ISO 14155)
Serious Adverse Event (SAE)	An adverse event that led to serious deterioration in the health of the patient, that either resulted in: • death • a life-threatening illness or injury • a permanent impairment of a body structure or a body function • in-patient or prolonged hospitalization • medical or surgical intervention to prevent life-threatening illness or injury • led to fetal distress, fetal death or a congenital abnormality or birth defect A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155) Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.
Product Complaint (PC)	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product after it is released for distribution or related to a service that affects the performance of such product. A complaint may involve the possible failure of the product itself, its packaging, or its labeling (i.e., product label, package insert, or any instructions for use). The complaint need not be confirmed by the manufacturer to be considered a complaint.
Serious Adverse Device Effect (SADE)	A serious ADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. (ISO 14155)
Unanticipated Serious Adverse Device Effect (USADE)	Any serious adverse device effect on health or safety or 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 investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients. (21 CFR 812.3(s))

Table 3. Definition of Terms

Term	Definition
Investigational product	For this protocol, the term "investigational product" is synonymous with Theranova 400 dialyzer.
Comparator product	For this protocol, the term "comparator product" is synonymous with Elisio-17H dialyzer.
Date of Onset	The date when the signs and symptoms of the AE begin.
Signs & Symptoms vs Diagnosis	If a definitive diagnosis has been medically established by the physician caring for the patient or by the Investigator, this diagnosis should then be recorded as the AE. If a definitive diagnosis has not been medically established, the signs and symptoms should then be recorded as the AEs.
Diagnosis vs Complications	A patient experiences not only a diagnosis, but also additionally a complication of the diagnosis (i.e., myocardial infarction with congestive heart failure); both the diagnosis and the medical complication should be collected and recorded as separate AEs.
Awareness Date or Baxter Awareness Date	The date on which any Baxter employee or their agent becomes aware of an AE. This date is considered Day 0 on the regulatory reporting time clock.

7.2 Safety Reporting

All AEs and PCs observed by the study personnel or reported by the patient during the course of the study will be documented from the time of signing the ICF (i.e. enrollment) through the end of study visit.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded 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.

Laboratory and vital sign abnormalities qualify as AEs if medical intervention is required to treat or address the abnormality, if the patient must be discontinued from the study due

to the abnormality, or if the value exceeds specific limits defined by the standard-of-care as qualifying it as an AE.

If a patient experiences a diagnosis, but also additionally a complication of the diagnosis (i.e., myocardial infarction with congestive heart failure); both the diagnosis and the medical complication should be collected and recorded on eCRFs as separate AEs.

Adverse events that change in severity will be documented as an additional AE to allow an assessment of the event at each level of severity.

If an AE or PC occurs, a full description of the event should be recorded including the date and time of onset, as well as outcome, seriousness, severity, event description, actions taken, and causal relationship of the AE. Investigators should review and reference the severity (see Table 4) and causality definitions (see Table 5) when determining relationship of the AE or PC to the study product. The investigators may also discuss the event(s) with the Baxter Medical Monitor or designee.

All AEs and PCs should be actively solicited and, no matter how common they are for a particular patient and regardless of the causality assigned by the Investigator. Additionally, any AE voluntarily reported by the patient should be recorded and verified by the Investigator or designee with the relevant source documents and eCRF pages. Supporting source documents should be de-identified. Each SAE will be documented on a separate SAE report form.

The outcome/resolution of all AEs will be determined by the Investigator and documented on the AE eCRF report form. Investigators will be instructed to follow all AEs as follows: Unrelated AEs will be followed until resolution or until the end of the study whichever comes first. Adverse device effects (related AEs) and all SAEs (related or not) will be followed until resolution or they become stable, including following the patient after the end of study if necessary.

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

For the outcome categories that can be used on the eCRF by the Investigator please refer to Table 6.

Table 4. Severity Assessments

Criterion	Definition
Mild	Is a transient discomfort and does not interfere in a significant manner with the patient's normal functioning level. The AE resolves spontaneously or may require minimal therapeutic intervention.
Moderate	Produces limited impairment of function and can require therapeutic intervention, but produces no sequelae.
Severe	Results in a marked impairment of function and can lead to temporary inability to resume usual life pattern. The AE produces sequelae requiring (prolonged) therapeutic intervention.

Table 5. Causality Assessment

Classification	Causality Criteria	Causal Association
Probably Associated	Event or laboratory test abnormality, with reasonable time relationship to medical device use Unlikely to be attributed to disease, procedure or other drugs/devices used Response to withdrawal clinically reasonable Re-challenge not required	YES
Possibly Associated	Event or laboratory test abnormality, with reasonable time relationship to medical device use Could also be explained by disease, procedure or other drugs/devices used Information on device withdrawal may be lacking or unclear	YES
Unable to Determine	Clinical event or laboratory test abnormality cannot be judged because information is insufficient or missing Data cannot be supplement or verified	YES
Unlikely Associated	Event or laboratory test abnormality, with a time to device use that makes a relationship improbable (but not impossible) Disease, procedure or other drugs/devices used provide plausible explanations	NO
Not Associated	Event or laboratory test abnormality, with a time to device use that makes a relationship impossible Disease, procedure or other drugs/devices used provide plausible explanations	NO

Table 6. Outcome Conclusion

Criteria
Death
Permanent Injury
Disease Aggravation
Resolved without Medical Intervention
Resolved with Medical Intervention
Ongoing
Unknown

7.2.1 Serious Adverse Events (SAEs) and Product Complaint (PC) Reporting

The PI shall:

- Record every AE and observed PC, together with an assessment,
- Report to Baxter or designee, within 24 hours, all SAEs and PCs that could have led to a serious adverse device effect (SADE),
- Report to the IRB SAEs and PCs that could have led to a SADE if required by the national regulations or by the IRB,
- Supply Baxter or designee, upon Baxter's or designee's request, with any additional information related to the safety reporting of a particular event,
- Report any SAE if becoming aware after study completion of an SAE or PCs that could have led to a SADE that occurred in a patient during their participation in the study, the SAE must be reported on the SAE Form within 24 hours after awareness.

Baxter or designee shall report to regulatory authorities, SAEs and PCs that could have led to a SADE, as required by the national regulations.

7.2.1.1 Anticipated Adverse Events Related to Theranova and Hemodialysis

Anticipated Adverse Events related to the device or therapy can be found in the Investigator's Brochure (IB), investigational plan or application (including a supplementary plan or application).

7.2.2 Product Complaints/Product Issues

Any product complaints identified by the investigator or designee will be recorded in the PCs form and forwarded to Baxter within 5 days of becoming aware.

7.3 Medical Monitor

The medical monitor will regularly review data collected from eCRFs for potential safety concerns. A formal review plan of aggregate AEs/SAEs and PCs will be documented in a study Safety Management Plan.

Periodic review of reported AEs will be completed by Baxter or designee. At the site level the Investigator must assess risk and clinical significance of events to each individual study patient, including removing the patient from the study if necessary.

7.4 Safety Reporting to Authorities and IRB

It is the responsibility of the Investigator to report any SAEs to IRB according to local regulatory requirements.

Baxter or designee will assess each SAE reported by the Investigator to determine if the event qualifies as an Expedited Report according to local regulations. Expedited safety reports and associated Investigator letters will be submitted to the appropriate Authority and the Principal Investigator by Baxter or designee. The Investigator will file this Investigator letter and Expedited Safety Report in their study file. Additionally, a copy of the Safety Report and Investigator Letter will need to be submitted by the Investigator to their IRB, as appropriate per local regulations.

8. STUDY ACTIVITIES

8.1 Schedule of Evaluations and Procedures

All clinical study evaluations will be performed according to Appendix 1 and the instructions listed below. If a patient discontinues from the study prematurely, every attempt will be made to perform all of the procedures and evaluations that are scheduled for the final visit (i.e. end of study visit).

8.2 Training for Theranova 400 dialyzer

Study personnel performing treatments with the Theranova 400 dialyzer for this clinical study will be comprised of physicians, HD nurses and other clinicians. Study staff will be trained on the use of the Theranova 400 dialyzer by the Sponsor’s representative prior to patient enrolment. Training dates and training material will be documented and filled in the Investigator Site File per GDP.

8.3 Training for Elisio-17H dialyzer

Training will be provided on Elisio-17H dialyzers as applicable.

8.4 Screening Period (Days –14 to -1)

Prior to performing any study procedures, an IRB approved ICF must be signed and dated by each study patient and the person who administered the ICF. Prior to participation in the trial, the patient will receive a copy of the signed/dated ICF. The original signed/dated ICF must be retained at the site and confirmation of informed consent documented in the patient's medical record. All IRB approved revisions to the ICFs must be signed/dated by all patients who are currently enrolled in the study. The patient will receive a copy of the signed/dated revised ICF. Patients will be instructed to sign, or initial the consent form using their legal names (not nicknames).

Signing of the ICF and the initial Screening visit may occur on the same day, if necessary.

8.4.1 Assessments and Procedures

After providing written informed consent, patients will enter the Screening period. The aim of the Screening period is to assess the eligibility of patients for randomization and participation in the study. The maximum duration of the Screening period is 2 weeks. Screening period of 2 weeks was designed to provide adequate time to obtain screening lab results and complete all screening procedures. This period may not be used to repeat tests if initial tests result in study exclusion.

A complete medical history will include a review for all major body systems and renal history (primary etiology of renal disease, and current HD prescription). Medical history will also include an assessment of all medications being taken at the time of Screening, and any ESA taken in the 30 days prior to Screening, with each medication having a corresponding indication recorded on the concomitant medication eCRF form. Treatment parameters as described in Section 8.5.1 will be collected during treatment visits.

Further assessments include:

- Demographics
- Physical examination
- Vital signs
- Pregnancy test for women with child bearing potential
- AEs/SAEs

- Clinical laboratory evaluation as outlined in Appendix 2
- Randomization

8.5 Treatment Period (Day 1 to Day 168)

Study treatment period will consist of 3 weekly in-center treatments over a period of 24 weeks, where patients will receive HD treatment with either the Theranova 400 dialyzer or Elisio-17H dialyzer.

Please refer to Appendix 1 for details of the Treatment Period activities and samplings.

8.5.1 Visit Procedures

Clinical laboratory evaluations will be taken at the first study dialyzer treatment and after every 4 weeks of treatment (i.e., Day 1 [first day of treatment], Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24).

On the day of the study visit, the following dialysis treatment data will be collected:

- Treatment parameters:
  - Programmed Q_B, Q_D and ultrafiltration flow rate (Q_{UF}); (all in mL/min)
  - Actual Total Ultrafiltration volume at end of treatment (mL/Session)
  - Q_B will be documented at the start, every 30 minutes, and at the end of every study treatment
  - Total dialysis time
- Duration of and reasons for any treatment interruptions
- Concomitant medications
- AEs/SAEs/ADEs/PCs
- PRO measurements (KDQOL-36 and EQ-5D-5L)
- Vital signs
- Pre- and post-dialysis body weight
- Clinical laboratory evaluation as outlined in Appendix 2

8.6 End of Study Visitor Early Termination Procedures

The following information will be collected and procedures or evaluations will be performed during the End of Study visit (first non-study treatment, Week 25) or Early Termination.

- Physical examination including weight
- Vital signs
- AEs/SAEs/ADEs/PCs
- Concomitant medications
- Clinical laboratory evaluation as outlined in Appendix 2

If a patient discontinues from the study prematurely, every attempt should be made to perform all of the procedures and evaluations that are scheduled for the End of Study visit.

9. DATA MANAGEMENT, QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted and that the data are generated, documented and reported in compliance with the protocol and applicable regulatory requirements. Quality control will be applied to all stages of data handling to ensure reliability and correct processing. The Sponsor is responsible for securing agreement from all involved parties to ensure direct access to all study related centers, source documents and reports for the purpose of monitoring and auditing. Agreements made with the Investigator/institution will be in writing.

9.1 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, International Conference on Harmonization (ICH) GCP, the IRB and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

10. PLANNED STATISTICAL METHODS

10.1 General Considerations

Further details of the planned statistical methods will be provided in the study statistical analysis plan (SAP). The purpose of the SAP is to further elaborate the statistical methods described in the protocol and describes analysis conventions to guide the statistical programming work. The SAP will be finalized at least two months prior to database lock. Any further clarification to the statistical methods described in the protocol will be documented in the SAP.

Unless otherwise noted, all analyses will be performed using SAS/GRAPH® 9.4 software, SAS/STAT® 14.1 software and Base SAS® 9.4. Copyright© 2002-2012, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. All Rights Reserved.

Differences between treatment groups will be evaluated at a two-sided significance level of 0.050 (when rounded to 3 decimal places) and p-values < 0.050 will be considered statistically significant, unless otherwise noted.

Baseline measure for laboratory assessments is defined as the last non missing value obtained prior to dialysis on the day of the first study treatment. The final measure for laboratory assessments is defined as the last non missing value obtained after the day of the first study treatment.

10.2 Determination of Sample Size

The sample size for this study is driven by the primary safety endpoint. The sample size calculation was performed using PASS® 15.0.1 software, procedure Non-Inferiority Tests for the difference between Two Means. Copyright© 2017, NCSS, LLC. All Rights Reserved. The power is based on a t-test with a one-sided alpha level of 0.025 where the true difference in means is assumed to be zero (0) and the non-inferiority margin is 5%.

Pre-dialysis serum albumin was not evaluated in the previous Theranova 400 dialyzer HD study, only the mass (G) of albumin in the dialysate was assessed. However, a study published in PLoS ONE[26] did use a prototype of the Theranova dialyzer (MCO-CI) where in pre-dialysis albumin levels were collected after a month of therapy and, based on these data, a mean and standard deviation (SD) of 35.3 and 3.7 was observed. Comparable pre-dialysis albumin levels are expected with both study dialyzers and with a sample size of 70 patients per group, a t-test with a 0.025 one-sided significance level will have 80% power to demonstrate non-inferiority of the Theranova 400 dialyzer compared to the Elisio-17H dialyzer as assessed by pre-dialysis serum albumin with a non-inferiority margin of 5%. To allow for 15% of patients to drop out, a total of 166 patients will be randomized 1:1 to treatment with the Theranova 400 dialyzer or treatment with the Elisio-17H dialyzer (i.e., 83 patients per group).

The 5% non-inferiority margin is based on results from 2 observational studies.[27,28] These studies looked at the association between serum albumin levels and mortality in large US cohorts of HD and PD patients, respectively. In both studies, variations in serum albumin of +/- 1 g/L over 6 months (corresponds to +/-0.1 g/dL) have been defined as “stable serum albumin levels”. A variation of +/- 1 g/L is a range with a width of 2 g/L, which is

larger than 5% if applied to the reported mean baseline serum albumin levels. Therefore, a 5% variation in serum albumin can be justified as having no clinical significance.

A previously conducted Theranova 400 dialyzer prototype HDF study (Comparison of the Clinical Performance of Two Theranova 400 Dialyzer Prototypes in Hemodialysis Mode with the Performance of a High-Flux Dialyzer in Hemodialysis Mode and a High-Flux Dialyzer in High-volume Hemodiafiltration Mode – A Pilot Study, registered at clinicaltrials.gov, NCT02377622) was used to obtain λ FLC reduction ratio mean and standard deviation (SD) of 37.8 and 8.26. With a total sample size of 140 evaluable subjects as determined based on the primary safety endpoint (70 in the Theranova 400 dialyzer treatment group and 70 in the Elisio-17H dialyzer treatment group), a difference of 4.56 in the λ FLC reduction ratio in favor of the Theranova 400 dialyzer can be detected with 90% power at a two-sided 0.05 significance level using a two-sided two-sample t-test assuming equal variances. The sample size calculation for the primary efficacy endpoint was performed using PASS® 15.0.1 software, procedure Two-Sample T-Test Assuming Equal Variance.

10.3 Analysis Populations

The Per-protocol (PP) set will include all randomized patients who have received at least three months treatment with a study dialyzer and do not have any major protocol violations that might impact the primary analyses.

The intent-to-treat full analysis (FA) set will include all randomized patients.

The primary analyses will be performed on the FA set and supported by an analysis using the PP set. All other analyses will be performed on the FA set unless otherwise noted.

10.4 Demographics and Baseline Characteristics

Continuous demographic and baseline characteristics including age, height, screening laboratory tests and screening vital signs will be summarized descriptively by treatment group and overall using sample size (N), mean, SD, minimum and maximum. A t-test will be used to evaluate mean differences between treatment groups or a non-parametric procedure, as appropriate.

Categorical demographic and baseline characteristics including gender, race and medical history will be summarized descriptively by treatment group using frequencies and percentages. Treatment group comparability will be evaluated using Fisher's exact test. Medical history; medical condition or surgery items collected on the eCRF will be coded

to the appropriate System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18 or higher.

10.5 Primary Endpoint(s)

The primary endpoints will be analyzed in a hierarchical manner, starting with the primary safety endpoint.

The primary analyses will be performed using a multiple imputation approach. Multiple imputations using SAS Proc MI will be used to impute missing data under the missing at random assumption and the data sets generated will be analyzed using SAS Proc MIANALYZE. It is expected that the missing values will be monotone (i.e., when a variable Y_j is missing for an individual i, then subsequent variables Y_k, $k > j$, are all missing for the individual i). Thus, the regression method for imputation will be used. Using the primary safety analysis as an example, if a subject is missing serum albumin values at weeks 20 and 24, a regression model is first fitted using the non-missing values prior to week 20 (baseline, weeks 4, 8, 12, and 16) in order to impute the missing value for week 20. This method is then repeated in order to impute the missing value for week 24 using the non-missing values of the prior weeks plus the newly imputed value for week 20.

Twenty complete data sets will be analyzed for the multiple imputation of the primary endpoint data. The impact of missing data on the primary safety and efficacy analyses will be further explored as sensitivity analyses using observed data as well as last observation carried forward.

10.5.1 Primary Safety Endpoint(s)

For the primary safety endpoint of pre-dialysis serum albumin after 24 weeks of treatment, let μ_T denote the Theranova dialyzer pre-dialysis serum albumin mean and let μ_R denote the Elisio-17H dialyzer pre-dialysis serum albumin mean. Then the null hypothesis to demonstrate non-inferiority using a 5% margin can be expressed as:

Ho: $\mu_T - \mu_R \leq -1.765$. The alternative hypothesis is expressed as Ha: $\mu_T - \mu_R > -1.765$.

An ANCOVA model with fixed effects of treatment and site and the continuous fixed covariate of baseline pre-dialysis serum albumin will be used to generate a two-sided 95% confidence interval (CI) for the difference in treatment means ($\mu_T - \mu_R$). If the lower bound is > -1.765 then non-inferiority will be demonstrated.

10.5.2 Primary Efficacy Endpoint(s)

For the primary efficacy endpoint of RR of λ FLC after 24 weeks of treatment, let μ_T denote the Theranova dialyzer RR of λ FLC mean at 24 weeks and let μ_R denote the Elisio-17H dialyzer RR of λ FLC mean at 24 weeks. Then the null hypothesis to demonstrate superiority can be expressed as:

Ho: $\mu_T - \mu_R = 0$. The alternative hypothesis is expressed as Ha: $\mu_T - \mu_R \neq 0$.

The primary safety analysis will be conducted first. If the primary safety analysis demonstrates non-inferiority, an ANCOVA model with fixed effects of treatment and site will be used to generate a two-sided 95% CI for the difference in treatment means ($\mu_T - \mu_R$). If the lower bound is > 0 then superiority will be demonstrated. The statistical testing of the primary efficacy endpoint of the reduction ratio (RR) of λ FLC after 24 weeks of treatment is contingent upon the outcome of the analysis of the primary safety endpoint and will only be conducted once non-inferiority could be established for the primary safety endpoint. This hierarchical testing approach guarantees that the overall type 1 error is controlled at a two-sided 0.05 significance level.

10.6 Secondary Endpoint(s)

10.6.1 Secondary Safety Endpoint(s)

Pre-dialysis serum albumin:

A Mixed-effect Model Repeated Measurement (MMRM) model will be used to evaluate differences between treatment groups in the change from baseline in pre-dialysis serum albumin after each four weeks of treatment. The model will include the fixed effect of treatment, visit; the continuous, fixed covariate of baseline measurement; and the random effect of patient.

Pre-dialysis serum albumin will be further categorized at baseline and final measurement into 4 categories: <3.5, ≥3.5-3.9, ≥4.0-4.4, ≥4.5. Shift tables will be generated to cross tabulate the number of patients within each category by treatment.

Pre-dialysis Factor VII, Protein C, Vitamin A, and Factor II:

An MMRM model will be used to evaluate the differences between treatment groups in the change from baseline in pre-dialysis Factor VII, Protein C, Vitamin A, and Factor II after 4 weeks and after 24 weeks of treatment. The model will include the fixed effect of treatment, visit; the continuous, fixed covariate of baseline measurement; and the random effect of patient.

nPNA (nPCR):
An MMRM model will be used to evaluate differences between treatment groups in nPNA(nPCR) collected after each 4 weeks of treatment. The model will include the fixed effect of treatment, visit, and the random effect of patient.

AEs, SAEs, and Product Complaints:
The summary of AEs will include AEs that occur on the day of or after the first study treatment. AEs will be mapped to a Primary SOC and PT according to MedDRA and summarized descriptively by SOC, PT and treatment group. Treatment group comparability in the incidence rates of adverse events will be evaluated using Fisher's exact test.

An overview (overall) summary table of all AEs will be generated that includes the total number of AEs, number and percentage of patients with at least one AE, number and percentage of patients with at least one SAE, number and percentage of patients with at least one severe AE, number and percentage of patients with at least one AE probably associated with study treatment, number and percentage of patients with an AE leading to study discontinuation and number and percentage of patients with an AE leading to death. This summary table will be presented by treatment group and combining both groups (Total).

Furthermore, separate AE summary tables will be provided by SOC and PT for SAEs and AEs leading to study withdrawal. Separate AE summary tables will be provided to show a breakdown of AEs by SOC, PT and

a. severity (mild, moderate or severe),
b. relationship to study treatment (probably related, possibly related, unable to determine, unlikely related or not related).

Study dialyzer related product complaints will be summarized descriptively by study dialyzer.

Chemistry and hematology:
Mean differences between treatment groups in the change from baseline to final measure in chemistry and hematology laboratory tests will be analyzed using an ANCOVA with a fixed effect of treatment and a fixed continuous covariate of baseline laboratory value.

10.6.2 Secondary Efficacy Endpoint(s)

In order to account for multiplicity, secondary efficacy analyses will be held to a hierarchical assessment and performed in the order outlined below. If the first analysis results in a p-value <0.05, then formal testing will continue to the second analysis. If the second analysis also results in a p-value <0.05, then formal testing will continue to the third analysis, and so on. This method of hierarchical assessment will continue until an analysis results in a p-value > 0.05, i.e., is considered statistically insignificant. This hierarchical approach guarantees that the overall alpha will not exceed 0.05.

1. MMRM of reduction ratio of λ FLC
2. MMRM of reduction ratio of CFD
3. MMRM of reduction ratio of κ FLC
4. MMRM of reduction ratio of IL-6
5. MMRM of reduction ratio of TNFα
6. MMRM of reduction ratio of β_2-microglobulin
7. Change in pre-dialysis β_2-microglobulin from baseline to 24 weeks
8. MMRM of Kt/V_{urea}

An MMRM model will be used to evaluate differences between treatment groups in the reduction ratios of λ FLC, CFD, κ FLC, IL-6, TNFα, β_2-microglobulin after 4 weeks and after 24 weeks of treatment. The model will include the fixed effect of treatment, visit, and the random effect of patient.

An ANCOVA with a fixed effect of treatment and a fixed continuous effect of baseline pre-dialysis β_2-microglobulin will be used to evaluate differences between treatment groups for the change from baseline in pre-dialysis β_2-microglobulin after 24 weeks of treatment.

An MMRM model will be used to evaluate differences between treatment groups in Kt/V_{urea} collected after each 4 weeks of treatment. The model will include the fixed effect of treatment, visit, and the random effect of patient.

10.7 Exploratory Endpoints

An MMRM model will be used to evaluate differences between treatment groups in the change from baseline in pre-dialysis serum levels of hs-CRP after each 4 weeks of treatment. The model will include the fixed effect of treatment, visit, as well as the continuous, fixed covariate of baseline measurement and the random effect of patient.

An MMRM model will be used to evaluate differences between treatment groups in the change from first day of treatment in KDQOL-36 and EQ-5D-5L after 12 weeks and after 24 weeks of treatment. The model will include the fixed effect of treatment, visit, as well as the continuous, fixed covariate of screening measurement and the random effect of patient.

Appropriate models will be used to evaluate differences between treatment groups in the utilization for medications (i.e., ESA, anti-hypertensives, iron).

10.8 Interim Analysis

An interim analysis will be conducted when 60% of enrollment is completed. The purpose of the interim analysis is a blinded sample size reassessment using the approach by Friede and Kieser[29] for an absolute difference in means which is based on the observed one-sample standard deviation calculated from the pooled data across treatment groups. This blinded sample size reassessment will be carried out by an independent statistician (who otherwise is not involved in the study conduct) using the 8 week measurements of the pre-dialysis serum albumin levels after 100 total patients have been enrolled (assuming 15% drop out, this corresponds to 84 evaluable patients). In case the observed pooled standard deviation at 8 weeks is larger than the assumed standard deviation of 3.7, the method will require an increase in overall sample size in order to maintain an overall power of 80%. If the observed standard deviation is smaller than the assumed standard deviation of 3.7, the overall sample size will be kept at 166.

11. ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

The study administrative structure of the study is described in Table 7. Ultimately it is the investigator who is responsible for the conduct of all aspects of the study at the study center.

Table 7. Study Administrative Structure

Role	Person Responsible
Sponsor:	Baxter Healthcare Corporation
Medical Monitor:	[redacted]
Project Manager:	[redacted]
Therapeutic Area Expert:	[redacted]
Statistician:	[redacted]

Table 7. Study Administrative Structure

Role	Person Responsible
Medical Writer[a]	[redacted]

[a] Considered an author of this protocol.

11.2 Institutional Review Board Approval

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

The Sponsor or its designee will supply relevant documents for PIs to submit to their respective IRB for review and approval of the protocol. The Investigator will not enroll patients into the study until the Investigator has received written approval for, or written favorable opinion on, the protocol, the informed consent document(s), and any patient-facing materials from their IRB. The IRB approval must refer to the study by exact protocol title, number, and version date; identify version of other documents (e.g., patient or care partner ICFs) reviewed; and state the approval date. The Investigator will make all required progress reports to their IRB in writing in a timely manner and will obtain all required approvals in writing (at least annually in all cases) to continue to participate in the study.

The Investigator will promptly report to their IRB any unanticipated problems associated with the study devices involving risks to patients or others, whether encountered at their site or provided as a safety report by Baxter.

The Investigator will promptly notify their IRB of any protocol amendment and will not implement any protocol amendment until the IRB has provided written approval of, or written favorable opinion on, the amendment.

11.3 Food and Drug Administration

The sponsor is in charge of submissions to FDA.

The Baxter Project Manager must receive a copy of the Investigational Device Exemption (IDE) approval document supplied by the FDA, prior to the inclusion of patients in the study and before sending investigational products to study sites.

11.4 Ethical Conduct of the Study

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

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

11.5 Patient Information and Consent

Preparation of the ICF is the responsibility of the PI and must include all elements required by GCP and applicable regulatory requirements and must adhere to GCPs and to ethical principles that have their origin in the Declaration of Helsinki. All ICFs will be reviewed by the Sponsor prior to IRB approval.

In all respects, the consent form must comply with Title 21, Part 50 of the CFR and ICH GCP 4.8, which both pertain to informed consent.

11.6 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. Patient medical information obtained for the purposes of this study is confidential and disclosure to third parties, other than Health Authority representatives, Baxter representatives, or the site's IRB, is prohibited. Patients should not be identified by name or medical record number on any documents or materials (samples, slides) sent to Baxter or its representatives or during verbal communications. Patients should be identified only by the study-assigned unique patient identification number.

To help maintain patient confidentiality, each patient will be assigned a unique patient identification number. Furthermore, only the site Investigator and designated site staff will have access to patient identifying information. All data will be compiled to construct a dataset comprising unique patient identification numbers in lieu of specific patient identifying data; study datasets shared outside of Baxter will be password-protected. While there is always a risk of loss of privacy when participating in a research program, reasonable efforts will be made to ensure the confidentiality of patient data. Under no circumstances shall any patient identifying information be shared with or disclosed to a third party for promotional uses. As stated above, the patient must be informed that his/

her personal study-related data will be used by Baxter and its representatives in accordance with country law or local IRB data protection directives.

11.6.1 HIPAA Authorization Procedures

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

11.7 Study Monitoring

The sponsor team or designee will monitor the study data on site and remotely as part of safety management and clinical monitoring. Monitoring will occur at regularly scheduled intervals at the study site to allow for verification by sampling of source documents and comparing these with information recorded on the eCRFs. In addition, eCRFs will also be monitored remotely during the course of study participation. Full details on eCRF monitoring will be specified in the Clinical Operations Plan.

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

More detailed information about Study Monitoring can be obtained from the Clinical Operation Plan.

11.8 Case Report Forms and Study Records

All clinical data associated with this study will be collected and reported electronically via a web address and secure password. The database will be housed on a physically and logically secure computer server maintained in accordance with written security policies.

The EDC system meets approved established standards for the security of health information and is validated per 21 CFR Part 11. The system also meets the ICH guideline E6R1 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained. Patient identifying information will not be included in the database, but must be maintained in a secure fashion at the Investigator site.

11.9 Protocol Violations/Deviations

The Investigator will not deviate from this protocol except in cases of medical emergency. The Investigator may deviate from the protocol without prior approval only when the change is necessary to eliminate an apparent immediate hazard to the patient. In that event, the Investigator will notify the Sponsor immediately by phone, notify the IRB and confirm notification to the Sponsor in writing as soon as possible, but within 5 working days after the change is implemented.

Protocol violations/deviations will be documented in source documentation, the Investigator's research study files, as applicable, and also recorded in the EDC. Baxter will be responsible for the Protocol Deviations master list. The clinical team will review deviations at a study level on a regular basis.

11.10 Access to Source Documentation

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

11.11 Data Generation and Analysis

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

Electronic Investigator signatures will be used to attest to the accuracy of data entered into the EDC system. The Study Monitor, in collaboration with the Investigators, must ensure that data entered into the EDC system are correct. Computerized data checks will be used to supplement manual review to check for data omissions, inconsistencies and

out of range values. An electronic audit trail system will be used to track all changes in the database.

Data management will be carried out by Baxter Global Science and Technology, Biometrics department or assigned designee.

Baxter or their assigned designee is responsible for the creation of the study eCRF and the associated electronic study database.

11.12 Retention of Data

The PI will retain study records and data in paper or electronic form in compliance with applicable regulatory requirements and for at least 15 years after the completion of the clinical trial. The PI must contact the Sponsor before destroying any records associated with the study. The Sponsor or its designee will notify the PI when the trial records are no longer needed. If the PI withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another PI, IRB). Baxter will be notified in writing of any such transfer.

11.13 Financial Disclosure

The financial aspects of the study will be documented in an agreement between the Sponsor and the Investigator.

11.14 Publication and Disclosure Policy

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

The data generated by this clinical study are the property of the sponsor. This data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor’s discretion or for submission to regulatory agencies. In addition, the sponsor reserves the right of prior review and approval of data from this study relative to the potential release of proprietary information to any publication or for any presentation.

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Appendix 1 Schedule of Evaluations and Procedures

		Treatment Period														
	Screening Visit	Visit 1 1st Treatment Day		Visit 2 Week 4		Visit 3 Week 8		Visit 4 Week 12		Visit 5 Week 16		Visit 6 Week 20		Visit 7 Week 24		End of Study Visit
Evaluation	**Days -14 to -1**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	
Informed consent	X															
Demographics	X															
Medical histories (past and present)	X															
Physical examination including weight[a]	X															X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[b]	X															
AE/SAE/ADE/PC[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HD prescription and Ultrafiltration[e]	X		X		X		X		X		X		X		X	
Body weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluations[f]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Reported outcomes[g]			X						X						X	

Note: All sampling visits will be performed during the mid-week treatment

[a] Weight will be measured at screening and end of study, height will be measured only at screening

[b] Eligible patients will be randomized at the end of the Screening Period

[c] AEs, SAEs and PCs will be collected after the informed consent is signed and throughout the study, until the end of study visit ADEs will be collected throughout the treatment period

[d] Medications will be collected throughout the study

[e] Ultrafiltration (UF) will be obtained at the end of treatment of each 4 week treatment period

[f] Collection of laboratory samples is presented in the Schedule of Clinical Laboratory Evaluations below

[g] Patient reported outcomes (PROs) will include KDQOL-36 and EQ-5D-5L All PROs will initially be assessed during the first treatment day, after 12 weeks of treatment and at the end of the study, following 24 weeks of treatment

Appendix 2 Schedule of Clinical Laboratory Evaluations

	Screening Visit Days -14 to -1		Treatment Period														End of Study Visit	
			Visit 1 1st Treatment Day		Visit 2 Week 4		Visit 3 Week 8		Visit 4 Week 12		Visit 5 Week 16		Visit 6 Week 20		Visit 7 Week 24			
Evaluation	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**
β-hCG[a]	X																	
λ FLC[b]	X		X		X	X									X	X		
β2 Microglobulin			X		X	X									X	X		
Serum Albumin	X		X		X		X		X		X		X		X		X	
Liver function[c]	X								X								X	
CFD[d]			X		X	X									X	X		
IL-6			X		X	X									X	X		
TNFα			X		X	X									X	X		
κ FLC[b]	X		X		X	X									X	X		
Vitamin A			X		X										X		X	
BUN	X	X			X	X	X	X	X	X	X	X	X	X	X	X		
Factor VII			X						X						X		X	
Protein C			X						X						X		X	
Factor II			X						X						X		X	
hs-C-Reactive Protein	X		X		X		X		X		X		X		X			
Hematology[e]	X		X						X								X	
HAV[f], HBV[g], HCV[h], HIV[i]	X																	

Coagulation[j]	X								X								X	
Serum phosphorus	X		X						X								X	
Comprehensive metabolic panel[k]	X		X						X								X	
Lipids[l]	X		X						X								X	

Notes: All sampling visits will be performed during the mid-week treatment

A serum beta human chorionic gonadotrophin (β-hCG) will be performed within 3 weeks prior to the 1st treatment in the study for women of childbearing potential

[a] Female subjects of childbearing potential, defined as a woman <55 years old who has not had a partial or full hysterectomy or oophorectomy, must have a negative serum β-hCG pregnancy test at Screening Subjects of childbearing potential must use a medically acceptable means of contraception during their participation in the study

[b] Lambda free light chains and Kappa free light chains

[c] Include: Alkaline phosphatase (ALK-P), Alanine aminotransferase (ALT; SGPT), Aspartate aminotransferase (AST; SGOT), and Gamma-glutamyl-transferase (GGT), total bilirubin, direct bilirubin, globulin, total protein

[d] Complement Factor D

[e] Includes: Hemotocrit, Hemoglobin, Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Mean corpuscular volume (MCV), Platelet count, Red blood cell (RBC) Count, White blood cell (WBC) Count with Differential

[f] Hepatitis A Virus

[g] Hepatitis B Virus

[h] Hepatitis C Virus

[i] Human Immunodeficiency Virus

[j] Includes: PT (INR), PT (Sec), aPTT

[k] Includes: Sodium, Potassium, Chloride, Calcium, Bicarbonate, Glucose, Creatinine

[l] Includes: Total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides

Appendix 3 Formulas for Calculation of Endpoints

Reduction Ratios (RR)

The RR for each solute, based on the change in the arterial plasma concentration over the dialysis session, will be calculated as:

$$RR\ (\%) = \left(1 - \frac{C_{Post}}{C_{Pre}}\right) \times 100$$

where C_{Pre} and C_{Post} are measured arterial plasma concentration of the solute before and after dialysis, respectively.[c]

However, for the middle molecules (λ FLC and β_2-microglobulin) C_{Post} will be first corrected ($C_{Post\text{-}corr}$) for the decrease in total extracellular volume due to fluid removal, as follows:

$$C_{Post-corr} = \frac{C_{Post}}{(1 + \frac{BW_{Pre} - BW_{Post}}{0.2 \times BW_{Post}})}$$

where C_{Post} is the measured plasma concentration of the solute after dialysis; and BW_{Pre} and BW_{Post} are the patient's body weight before and after dialysis, respectively.[d]

Kt/V_{urea} (quantification of hemodialysis treatment adequacy)

The linear equation used to calculate Kt/V_{urea} when applied to HD administered 3 times a week is as follows:

$$\frac{Kt}{V} = -\ln(R - 0.008 \times T) + (4 - 3.5 \times R) \times 0.55 \times \frac{Weightloss}{V}$$

where R is the ratio of post-dialysis to pre-dialysis BUN; V is the body water volume and Weightloss is expressed in the same units; and T is treatment time in hours.[ef]

[c] Krieter DH, Lemke HD, Wanner C. A new synthetic dialyzer with advanced permselectivity for enhances low-molecular weight protein removal. *Artif Organs*. 2008;32(7):547-554.
[d] Bergström J, Wehle B. No change in corrected β2-microglobulin concentration after cuprophane haemodialysis. *Lancet.* 1987;1:628-629.

nPNA (nPCR)

The below equations are used to calculate the midweek PNA (PCR) when applied to HD patients is as follows:

$$PNA\ (PCR) = \frac{C_0}{\left[25.8 + \left(\frac{1.15}{\frac{spKt}{V}}\right) + \frac{56.4}{\frac{spKt}{V}}\right]} + 0.168$$

where C_0 is the pre-dialysis BUN.

SpKt/V is calculated as per below equation:

$$\frac{spKt}{V} = -Ln(R - 0.008 \times t) + \left(4 - (3.5 \times R)\right) \times \frac{UF}{W}$$

where R is the post-dialysis/pre-dialysis BUN, t is the dialysis session in hours, UF is the ultrafiltration volume in liters, and W is the post-dialysis weight in kilograms.[g]

V is calculated as per Watson formulas below:

$$Males\ V = 2.447 - (0.09516 \times age) + (0.1074 \times height) + (0.3362 \times weight)$$

$$Females\ V = -2.097 + (0.1069 \times height) + (0.2466 \times weight)$$

where V is the total body water.[h]

PNA should be normalized to adjust to a specific body size. This will be done using the formula below:

$$nPCA(nPCR)\left(\frac{\frac{g}{kg}}{d}\right) = (PNA)/(\frac{V}{0.58}))$$

[e] National Kidney Foundation. KDOQI Clinical Practice Guideline for Hemodialysis Adequancy: 2015 Update. *Am J Kidney Dis.* 2015;66(5):884-930.
[f] Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol.* 1993;4(5):1205-1213.
[g] Depner TA, Daugirdas T. Equations for Normalized Protein Catabolic Rate Based on two-Point Modeling of Hemodialysis Urea Kinetics. *J Am Soc Nephrol.* 1996;7:780-785.
[h] National Kidney Foundation. NKF_DOQI Clinical Practice Guidelines: Measurement of dialysis adequacy. *Am J Kidney Dis.* 1997;30(2):S22-S31.

Appendix 4 Sponsor Signatures

Study Title:	A Multi-Center, Prospective, Randomized, Controlled, Open-label, Parallel Study to Evaluate the Safety and Efficacy of the Theranova 400 Dialyzer In End Stage Renal Disease (ESRD) Patients
Study Number:	**7905001**
Final Date:	2017 JUN 12
Amendment 1:	2017 JUL 25
Amendment 2:	2017 AUG 31
Amendment 3:	2017 OCT 11
Amendment 4:	2017 OCT 25
Amendment 5:	2018 FEB 09

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: _____

[redacted], MD, PhD
[redacted]
Clinical and HEOR
Baxter Healthcare Corporation

Signed: _____ Date: _____

[redacted], PhD
[redacted]
Global Medical Affairs
Baxter Healthcare Corporation

Signed: _____ Date: _____

[redacted]
Biometrics / Clinical and HEOR
Baxter Healthcare Corporation

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Global Regulatory Affairs
Baxter Healthcare Corporation

Signed: [redacted] Date: [redacted]

Clinical and HEOR
Baxter Healthcare Corporation

Appendix 5 Investigator's Signature

Study Title:	A Multi-Center, Prospective, Randomized, Controlled, Open-label, Parallel Study to Evaluate the Safety and Efficacy of the Theranova 400 Dialyzer In End Stage Renal Disease (ESRD) Patients
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Amendment 3:	2017 OCT 11
Amendment 4:	2017 OCT 25
Amendment 5:	2018 FEB 09

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

Signed:_____ Date:_____