Statistical Analysis Plan: 7905001

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
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.
Product Name:	Theranova 400 Dialyzer
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.
Statistician:	[redacted] [redacted] Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015
Sponsor:	Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015
Responsible Medical Officer:	[redacted], MD, MS, FAAP
Final Date:	2018 NOV 16
Version:	2.0

[redacted]

[redacted]

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1. SIGNATURE PAGE

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

Statisticians: [redacted]

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

Prepared by: [redacted] Date: [redacted]

[redacted]

Baxter Healthcare Corporation

Approved by: _____ Date: _____

[redacted]

Baxter Healthcare Corporation

Approved by: _____ Date: _____

[redacted], MD, MS, FAAP

[redacted]

Baxter Healthcare Corporation

1. SIGNATURE PAGE

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Prepared by: _____ Date: _____
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Approved by: [redacted] Date: [redacted]
[redacted]
Baxter Healthcare Corporation

Approved by: _____ Date: _____
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[redacted]
Baxter Healthcare Corporation

[redacted]

1. SIGNATURE PAGE

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Study Number:	7905001
Statisticians:	[redacted]

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

Prepared by:_____ Date:_____

[redacted]
Baxter Healthcare Corporation

Approved by:_____ Date:_____

[redacted]
Baxter Healthcare Corporation

Approved by:_____ Date:_____

[redacted], MD, MS, FAAP
[redacted]
Baxter Healthcare Corporation

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADE	Adverse Device Effect
AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
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
FAS	Full Analysis Set
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
ITT	Intention-to-treat
LOCF	Last Observation Carried Forward
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
PPS	Per-Protocol Set
PRO	Patient Reported Outcome
PT	Preferred Term
PUR	Polyurethane
Q_B	Blood Flow Rate
Q_D	Dialysate Flow Rate
RCT	Randomized Clinical 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

3. INTRODUCTION

This Statistical Analysis Plan is intended to describe the planned statistical analysis of study 7905001.

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.[1]

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.[2-5] 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.

4. TRIAL OBJECTIVES

The purpose of this study is to provide data on the safety and efficacy of Theranova 400 dialyzer compared Elisio-17H dialyzer in subjects with ESRD who have been stable and receiving hemodialysis (HD) therapy at least 3 times a week for 3 months prior to enrollment.

4.1 Primary Objectives

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.

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).

4.2 Secondary Objectives

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.

4.3 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.

5. STUDY DESIGN AND CONDUCT CONSIDERATIONS

5.1 Study Design

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 consequent three (3) 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 will be performed on monthly basis.

5.2 Baseline Definition

Baseline measure for laboratory assessments and vital signs is defined as the last pre-dialysis 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 value

captured during study treatment sessions (Week 24). If laboratory assessment on Week 24 is not applicable, the value on end of study visit (pre-dialysis) will be considered as final measurement.

Baseline measure for demographics, physical examination, general medical history and renal medical history is obtained during screening.

5.3 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[6] 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).

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. Including 15% drop out, a total sample size of 166 (83 per treatment group) need to be enrolled into this study.

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.

5.3.1 Justification of Non-Inferiority Margin

The 5% non-inferiority margin for reduction of albumin is based on two observational studies (Kalantar-Zadeh 2005[7] and Mehrotra 2011[8]) in which a longitudinal analysis (change over time) of the association between serum albumin levels and mortality in large US cohorts of HD and PD patients, respectively, has been performed. Both studies controlled for underlying confounders of mortality by adjusting for comorbidities and Malnutrition-Inflammation Complex Syndrome. In both studies, variations in serum albumin levels 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.

The longitudinal analysis performed by Kalantar-Zadeh 2005 in 30,827 HD patients came to the conclusion that when comparing a reference group with serum albumin values in the range of 3.6 – 3.79 g/dL to groups of patients with ranges of serum albumin levels that were 0.2 g/dL (i.e. ≥5% of the center of reference range) apart from the reference range, no increase in hazard ratio for all-cause and cardiovascular death was found.[7]

So, if we demonstrate statistically that the mean pre-dialysis serum albumin level of the Theranova group is unlikely to decrease by more than 5% after 24 weeks of therapy compared to control group, it can be hypothesized that the mortality risk associated with a decrement in serum albumin levels is not higher for the Theranova group. Therefore, a 5% non-inferiority margin is appropriate from a clinical point of view.

5.4 Randomization Procedure

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 one hundred and sixty-six (166) patients across up to thirty (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 Schedule of Visits and Procedures

All clinical study evaluations will be performed according to the 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).

Table 1. Schedule of Visits and Procedures

Evaluation	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		
		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 (U_F) will be obtained at the end of treatment of each 4 weeks 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.

5.5.1 Schedule of Clinical Laboratory Evaluations

Table 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	

[redacted]

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

5.6 Safety Measures

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) calculated after every 4 weeks of treatment.
- Change from baseline to final measure in chemistry and hematology laboratory tests (see Table 7 in Section 9.3).
- Monitoring of adverse events (AEs), serious adverse events (SAEs) and product complaints (PCs) for Baxter related devices.

5.7 Efficacy Measures

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.

5.8 Exploratory Measures

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 as cumulative dose for every 4 weeks' interval (i.e., erythropoiesis-stimulating agent (ESA), anti-hypertensive, iron and phosphate).

5.9 Completion and Discontinuation

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 events (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.

6. STUDY POPULATIONS

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.

6.1 Subject Disposition

The number of subjects who signed informed consent (enrolled), met the pre- and intra-operative inclusion and exclusion criteria (eligible), were randomized, and withdrew early will be displayed for subject disposition. Early withdrawals will be summarized according to primary reason for withdrawal. This table will be presented by treatment group and overall.

6.2 Analysis Populations

The full analysis set (FAS) will include all randomized patients.

The per-protocol set (PPS) will include all randomized patients who have received 24 weeks treatment with a study dialyzer without missing 3 consecutive study treatments (i.e. missing a full week of dialysis sessions) and do not have any major protocol violations that might impact the primary analyses.

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

FAS is presented as-treated for analyses of

- AEs, SAEs, and Product Complaints

For other analyses including primary, secondary and exploratory endpoints, FAS is presented as-randomized.

6.3 Protocol Deviations

Protocol deviations will be classified as minor or major deviations and reviewed at a data review meeting.

Subjects with any major protocol deviation that may impact the primary endpoints will be excluded from the per-protocol analysis set, including the following:

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

6.4 Subgroups

No subgroup analysis is planned for this study.

7. STATISTICAL ANALYSIS

The analyses described in this SAP refer to Amendment 5 of the Clinical Trial Protocol: 7905001 (dated 2018 FEB 09).

7.1 General

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

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.

The continuous data points will be summarized descriptively as mean, SD, median, min/max and categorical data points will be summarized as frequency and percentages.

7.2 Handling of Missing Data

7.2.1 General

Missed dialysis session visits will not be replaced. For dialysis sessions besides in Visit 8 Week 24, 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 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). Any dialysis session in Visit 8 Week 24 can not be collected behind schedule. Reasons for missed visits will not be captured separately but will be part of protocol deviation and/or as study discontinue reason if the patient being terminated from the study. Reasons for any other missing data besides missed visits will also be addressed via protocol deviations. A listing of protocol deviations will include a field showing whether the deviation lead to missing data. A protocol deviation table will summarize the number of missing data points in total and categorized by protocol deviation classification (major or minor).

7.2.2 Primary Analysis

The primary analyses will be performed using a multiple imputation approach. Multiple imputations using SAS Proc MI will be implemented to impute missing data under the missing at random assumption and the data sets generated will be analyzed using SAS Proc MIANALYZE.[9]

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

Multiple imputation inference involves three distinct phases:

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

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

A data set with variables $Y_1, Y_2, \ldots, Y_p$ (in that order) is said to have a monotone missing pattern when the event that a variable Y_j is missing for a particular individual implies that all subsequent variables Y_k, $k > j$, are missing for that individual.

For data sets with monotone missing patterns, the variables with missing values can be imputed sequentially with covariates constructed from their corresponding sets of preceding variables. The regression method (Rubin 1987, pp. 166-167)[10] 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 (20) complete data sets will be analyzed for the multiple imputation of the primary endpoint data.

7.2.3 Sensitivity Analysis

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 (LOCF).

7.3 Interim Analysis

An interim analysis after 60% of enrollment will be conducted. The purpose of the interim analysis is a blinded sample size reassessment using the approach by Friede and Kieser[11] for an absolute difference in means which is based on the observed one-sample standard deviation calculated from the pooled data across treatment groups (described in more detail, below). 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 or equal to the assumed standard deviation of 3.7, the overall sample size will be kept at 166.

We consider a two-sample situation comparing a test treatment (T) with a control (C). Suppose that $X_{T1}, X_{T2}, \ldots$ and $X_{C1}, X_{C2}, \ldots$ are series of independent normal observations with means μ_T and μ_C, respectively, and common unknown variance σ^2.

If the margin δ^D denotes the defined range for the difference of means, the corresponding non-inferiority test problem can be formulated as follow:

$H_0 : \mu_T - \mu_C \leq \delta^D$ versus $H_1 : \mu_T - \mu_C > \delta^D$

Here we denote σ^2 as the pooled variance estimate. The non-inferiority hypothesis H_0 can be rejected at level α. The total required sample size for the rejection of H_1 with power $1 - \beta$ at the specified alternative $\theta_D^* = \mu_T - \mu_C$ is approximated by

$$N_D = 4\frac{(z_{1-\alpha} + z_{1-\beta})^2}{(\theta_D^* - \delta^D)^2}\sigma^2$$

where z_{1-prob} denotes the value exceeded by a standard normal random variable with probability *prob*. (In this study, $\alpha = 0.025$ and $\beta = 0.2$.) The required sample size for the non-inferiority test problem H_0 versus H_1 is for $\theta_D^* = 0$ given by the N_D. Then this number should be first rounded up to the upper even integer limit considering it will be a total sample size of two groups (per-protocol set). Later, inflate it by 15% drop out rate and round up to upper even integer limit again. The final number will be recognized as the new total sample size (full analysis set). If the observed pooled SD is smaller than 3.7, the re-estimated sample size will be smaller than 140 (PPS) and 166 (FAS). In these cases, the overall sample size will remain at 166 (FAS). There will be no decrease of sample size.

Table 3. List of Tables and Listings for Interim Analysis

Table Number	Table Name
14.1.1	Subject Disposition
14.2.2	8 Week Albumin Overall Standard Deviation and Re-Estimated Sample Size Estimate

Listing Number	Listing Name
16.2.1.1	Patient Disposition
16.2.1.2	Inclusion and Exclusion Criteria
16.2.1.3	Reasons for Withdrawal Prior to 8-week Study Treatment
16.2.2	Protocol Deviations
16.2.8.1	Albumin Measurements

7.4 Pooling Strategy for Study Sites

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

7.5 Visit Windows/Unscheduled Visits

For tabulation, values will be summarized according to the planned time point as recorded in the eCRF. Data recorded at unscheduled visits will only be presented in listings.

7.6 Calculation of Total Scores for Patient Reported Outcome Measures

7.6.1 Kidney Disease and Quality of Life (KDQOL-36)

The KDQOL-36 questionnaire is a 36-question survey that assesses subjects' quality of life and general well-being as it relates to their kidney disease.

The scores in each question of the KDQOL-36 scale do not all point in the same direction. For some questions a higher score indicates a better quality of life, while for other questions a higher score indicates poorer quality of life. Therefore, to calculate total scores, the direction of the values for each question must be recoded prior to calculating the total score.

As such, the SAS procedure developed by the KDQOL Working Grouptzer[1,2], will be used to convert the raw scores to recoded scores and individual scale scores. A description of the recoding procedure is summarized in Table 4.

Table 4: Kidney Diesase and Quality of Life

Item Number	Original Response Category	To Recoded Value Of
1, 8, 17 – 36[a]	1 2	100 75

[redacted]

	3 4 5	50 25 0
2 – 3	1 2 3	0 50 100
4-7	1 2	0 100
9-10	1 2 3 4 5 6	100 80 60 40 20 0
11	1 2 3 4 5 6	0 20 40 60 80 100
12 - 16	1 2 3 4 5	0 25 50 75 100
[a] The answer for Question 28 will come from Question 28a on the survey (for hemodialysis patients only). Question 28b will not be included in the calculation since it only applies to peritoneal dialysis patients. If both Question 28a and 28b are populated, then the more severe score will be used.		

The recoded values will be subsequently classified as indicated in Table 5 to create the individual scale scores.

Table 5: Combining KDQOL-36 Items for Domain Scores

Scale	Combination[a] of Individual Questions
SF-12 Physical Health Composite	1 - 12
SF-12 Mental Health Composite	
Burden of Kidney Disease	13 - 16
Symptom, Problem List	17 – 28b
Effects of Kidney Disease	29 - 36

[a] For 'Burden of Kidney Disease', 'Symptom, Problem List', and 'Effects of Kidney Disease' the individual question scores will be averaged. For the remaining scale items, the questions will be combined into the corresponding scores as indicated by the SAS procedure developed by the KDQOL working group[12].

Calculation of an overall total score is not recommended by the KDQOL Working Group.[13] Instead, the results of the questionnaire are best interpreted by using the domain scores described above. As such, these domain scores will be used for analyses instead of a total score.

Since the individual scale scores are calculated as an average or combination of the contributing questions, if an answer to a question is missing then the domain score will still be calculated. If all the questions contributing to the individual scale score are missing, then the individual scale score will be missing.

Question 28 is composed of two parts: 28a is only to be answered by patients on hemodialysis and 28b is only to be answered by patients on peritoneal dialysis. In some cases, patients give answers to both items. If this is the case, the most extreme response of the two will be taken and used in the computation of the domain score as described above.

7.6.2 Health-Related Quality of Life Questionnaire (EQ-5D-5L)

The 5-level EQ-5D version (EQ-5D-5L) was introduced by the EuroQol Group[14] in 2009 to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the EQ-5D-3L. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement. EQ-5D-5L value sets are available for each country that performed a valuation study for the EQ-5D-3L (Table 6). By using the crosswalk link function and the individual responses to the EQ-5D-5L descriptive system, index

values for the EQ-5D-5L can be calculated. Documents containing information on the crosswalk project, tables of values for all 3125 health states and the 'EQ-5D-5LCrosswalk Index Value Calculator' can be downloaded from the EuroQol website.[15]

Table 6: Organizing EQ-5D-5L Data

Variable Name	Self-care	Activity	Pain	Anxiety	State	EQ_VAS[a]
Variable Description	1=No problems 2=Slight problems 3=Moderate problems 4=Severe problems 5=Unable to 9=Missing value	1=No problems 2=Slight problems 3=Moderate problems 4=Severe problems 5=Unable to 9=Missing value	1=No pain 2=Slight pain 3=Moderate pain 4=Severe pain 5=Extreme pain 9=Missing value	1=Not anxious 2=Slightly anxious 3=Moderately anxious 4=Severely anxious 5=Extremely anxious 9=Missing value	5-digit code for EQ-5D-5L	999=Missing value

[a] From 'EQ-5D-5LCrosswalk Index Value Calculator' downloaded from the EuroQol website based on values as US location.

7.6.3 Utilization for Medications

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.

Medication of erythropoiesis-stimulating agent (ESA), anti-hypertensives, iron and phosphate will be derived from concomitant medication from corresponding categories coded by WHO drug dictionary. Only quantifiable doses and frequencies will be included in analysis. For drugs having "tablet" or "as needed" will only be listed as concomitant

mediation. Cumulative dose for every 4 weeks' interval will be standardized by unit; and summarized descriptively (mean, SD, median, min, max) and change form baseline (i.e. cumulative dose from 4 weeks prior to study treatment and before 1st treatment day).

7.7 Other Issues

Not applicable.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Continuous demographic and baseline characteristics including age, height, screening laboratory tests, screening vital signs and renal medical history will be summarized descriptively by treatment group and overall using sample size (N), mean, SD, minimum and maximum. A t-test or Wilcoxon rank-sum test, as appropriate, will be used to evaluate potential differences in the distribution of the underlying demographic or baseline characteristics between treatment groups.

Categorical demographic and baseline characteristics including gender, race, ethnicity, general medical history and renal 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.

Information regarding the type and frequency of dialysis therapy received prior to enrollment in this study, and the type of access will be presented. 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.

9. TREATMENT COMPLIANCE AND EXPOSURE

Each patient should receive 73 study treatments during the 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.

The following information on the study dialysis will be tabulated by treatment group and visit and/or provided in a listing.

9.1 Study Treatment Information

- Study treatment date, start/end time (listing only)
- Dialyzer lot number (listing only)
- Actual treatment duration
- Blood flow rate (Q_B)
- Dialysate flow rate (Q_D)
- Ultrafiltration flow rate (Q_{UF})
- Actual total ultrafiltration volume at end of treatment
- Interruptions occurred during the treatment: reason (free text), start/end time for each interruption (listing only)

9.2 Vital Signs

- Date of Assessment (listing only)
- Temperature
- Pre- /post-dialysis weight
- Pulse
- Respiratory rate
- Systolic BP
- Diastolic BP

9.3 Clinical Laboratory Evaluations

- Date and time lab sample collected (listing only)
- Initial / re-test (listing only)
- Accession / sample number (listing only)

Table 7: List of Laboratory Tests

(Test on screening pre-dialysis):

- β-hCG (if applicable)
- Hepatitis A, B and C
- Human Immunodeficiency Virus

(Test on screening pre-dialysis, 1st treatment day pre-dialysis, week 4 pre-/post-dialysis and week 24 pre-/post-dialysis):

- λ FLC
- κ FLC

(Test on 1st treatment day pre-dialysis, week 4 pre-/post-dialysis and week 24 pre-/post-dialysis):

- β2-microglobulin
- CFD
- IL-6
- TNFα

(Test on 1st treatment day pre-dialysis, week 12 pre-dialysis, week 24 pre-dialysis and end of study pre-dialysis):

- Factor II
- Factor VII
- Protein C

Comprehensive Metabolic Panel (test on screening pre-dialysis, 1st treatment day pre-dialysis, week 12 pre-dialysis and end of study pre-dialysis):

- Bicarbonate

(Test on 1st treatment day pre-dialysis, week 4 pre-dialysis, week 24 pre-dialysis and end of study pre-dialysis):

- Vitamin A

(Test on every visit pre-dialysis besides end of study pre-dialysis):

- hs-CRP

Serum Chemistry:
(Test on every visit pre-dialysis):

- Albumin

(Test on every visit pre-/post-dialysis besides 1st treatment day and end of study):

- BUN

(Test on screening pre-dialysis, 1st treatment day pre-dialysis, week 12 pre-dialysis and end of study pre-dialysis):

- Phosphorus

Coagulation (test on screening pre-dialysis, week 12 pre-dialysis and end of study pre-dialysis):

- Prothrombin time
- INR
- Activated partial thromboplastin time

Hematology (test on screening pre-dialysis, 1st treatment day pre-dialysis, week 12 pre-dialysis and end of study pre-dialysis):

- Calcium
- Chloride
- Creatinine
- Glucose
- Sodium
- Potassium

Liver Function (test on screening pre-dialysis, week 12 pre-dialysis and end of study pre-dialysis):

- Alkaline phosphatase
- ALT; SGPT
- AST; SGOT
- Direct bilirubin
- Gamma-glutamyl transferase
- Globulin
- Total bilirubin
- Total protein

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

Lipids (test on screening pre-dialysis, 1st treatment day pre-dialysis, week 12 pre-dialysis and end of study pre-dialysis):

- 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

9.4 Physical Examination

- Examination Date (listing only)
- Weight
- Height (screening only)
- Edema Status (+1, +2, +3, +4)

10. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

The definition of final measure for laboratory assessments has been updated to the last value captured during study treatment sessions (Week 24). If laboratory assessment in Week 24 is not applicable, the value on end of study visit (pre-dialysis) will be considered as final measurement.

The definition of the per-protocol analysis set has been changed to patients who have received 24 weeks treatment with a study dialyzer, without missing 3 consecutive study treatments (i.e. missing a full week of dialysis); and do not have any major protocol violations that might impact the primary analyses. This update is more in alignment with the expectation of continuous treatment over 6 months period.

For the analyses of adverse events incidences of AEs will be compared between the two treatment groups in addition to the pre-planned analyses based on incidence rates.

In addition to the investigator's assessments of potential abnormal parameters which have been reported as AEs on eCRF, clinical significance will be displayed based on corresponding MedDRA System Organ Class.

The formula for the calculation of the midweek nPNA (nPCR) provided in Appendix 3 of the study protocol was transcribed incorrectly from the source. The correct version of the formula is included in Appendix 1 of this SAP. Safety Parameters

11. SAFETY PARAMETERS

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

11.1 Primary Analysis

For the primary safety endpoint of pre-dialysis serum albumin after 24 weeks of treatment, let μ_T denote the Theranova 400 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 (μ_T- μ_R). If the lower bound is > -1.765 then non-inferiority will be demonstrated.

The primary safety 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 (for more detail on missing data imputation see Section 7.2.2).

Twenty (20) complete data sets will be analyzed for the multiple imputation of the primary endpoint data.

The analysis of the primary safety endpoint will be carried out on both the FAS and PPS. The analysis using the PPS will be used as a supportive analysis.

11.2 Sensitivity Analysis

The impact of missing data on the primary safety analyses will be further explored as sensitivity analyses using observed data as well as last observation carried forward.

11.3 Secondary Analysis

The analysis of the secondary safety endpoints will be carried out on the FAS.

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 and 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 and incidence rates of adverse events will be evaluated using Fisher's exact test and Wald's method with normal approximation, respectively.[16] AEs that occur prior to 1st day of study treatment will only be listed.

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),
a. relationship to study treatment ("probably related", "possibly related", and "unable to determine" will be categorized as "related to study treatment" while "unlikely related" and "not related" will be categorized as "unrelated to study treatment").

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 week 24 pre-dialysis measure (if not applicable, end of study pre-dialysis measure will be used) 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. BUN will be analyzed in the change from pre-dialysis at screening to pre-dialysis after 24 weeks of treatment; further by BUN reduction ratio as compare to from screening to after 24 weeks of treatment.

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.

In addition to the investigator's assessments of potential abnormal parameters which have been reported as AEs on eCRF, clinical significance will also be displayed based on potential links to specific MedDRA System Organ Classes and Preferred Terms are indicative of abnormalities of lab values as derived by Baxter's Clinical Medical group's discretion.

12. EFFICACY PARAMETERS

Hypothesis testing of the primary efficacy endpoint will only be conducted if non-inferiority could be established for the primary safety endpoint. The analysis of the primary efficacy endpoint will be carried out on both the FAS and PPS. The analysis using the PPS will be used as a supportive analysis.

12.1 Primary Analysis

For the primary efficacy endpoint of RR of λ FLC after 24 weeks of treatment, let μ_T denote the Theranova 400 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 I error is controlled at a two-sided 0.05 significance level.

The primary efficacy 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 (for more detail on missing data imputation see Section 7.2.2).

Twenty (20) complete data sets will be analyzed for the multiple imputation of the primary endpoint data.

12.2 Sensitivity Analysis

The impact of missing data on the primary efficacy analyses will be further explored as sensitivity analyses using observed data as well as last observation carried forward.

12.3 Secondary Analysis

The analysis of the secondary efficacy endpoints will be carried out on the FA.

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 β2-microglobulin
7. ANCOVA of change in pre-dialysis β2-microglobulin from baseline to 24 weeks
8. MMRM of Kt/Vurea

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.

13. EXPLORATORY ANALYSES

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.

Cumulative doses in the utilization for medications (i.e., ESA, anti-hypertensive, iron and phosphate) over 4 weeks intervals across 24 weeks study treatment will be summarized descriptively. An MMRM model will be used to evaluate differences between treatment groups in the change from accumulation of 4 weeks prior to study treatment after 4, 8, 12, 16, 20 and 24 weeks study treatment. The analysis of the exploratory endpoints will be carried out on the FAS.

14. REFERENCES

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Appendix 1 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.[1]

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.[2]

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.[3][4]

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nPNA (nPCR)

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

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

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 in mg/dL, t is the dialysis session in hours, UF is the ultrafiltration volume in liters, and W is the post-dialysis weight in kilograms, height in centimeters.[5]

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.[6]

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Appendix 2 Exposure-Adjusted Incidence Rate

Exposure-adjusted incidence rate (EAIR), defined as the number of subjects with a specific event divided by the total exposure-time among the subjects in the treatment group and at risk of an initial occurrence of the event[7,8], Specifically,

$$EAIR = \frac{n}{T} = \frac{n}{\sum t_i}$$

where n is the number of subjects with events, t_i is a subjec's exposure time under a given unit and T is the total exposure time under a given time unit of the subject. If a subject has multiple events, the t_i is the time of the first event. For a subject with no event, the t_i is censored at the last follow-up time for that subject. The definition of EAIR is based on the assumption that the occurrences of a specific event are following an independent Poisson process, so the event occurs with a constant rate over time.

Use the same 2×2 contingency table as before, the test statistic is given by

$$E = \left(\frac{n_{11}}{T_1} - \frac{n_{12}}{T_2}\right) / \sqrt{\frac{n_{11}}{T_1^2} + \frac{n_{12}}{T_2^2}}$$

Which follow the standard normal distribution under the null hypothesis.

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Appendix 3 Clinical Laboratory Evaluation Name Mapping

Table 8: Clinical Laboratory Evaluation Name Mapping

Clinical Laboratory Evaluation Name in Protocol	Clinical Laboratory Evaluation Name in CDSIC
APTT	Activated Partial Thromboplastin Time
Alanine aminotransferase (ALT; SGPT)	Alanine Aminotransferase
Serum albumin	Albumin
Alkaline phosphatase (ALK-P)	Alkaline Phosphatase
Aspartate aminotransferase (AST; SGOT)	Aspartate Aminotransferase
Basophils	Basophils
Basophils (%)	Basophils (%)
β2-Microglobulin	Beta-2 Microglobulin
Bicarbonate	Bicarbonate
Total Bilirubin	Bilirubin
Calcium	Calcium
Chloride	Chloride
Total Cholesterol	Cholesterol
β-hCG	Choriogonadotropin Beta
Creatinine	Creatinine
Direct Bilirubin	Direct Bilirubin
Eosinophils	Eosinophils
Eosinophils (%)	Eosinophils (%)
Mean corpuscular hemoglobin concentration (MCHC)	Ery. Mean Corpuscular HGB Concentration
Mean corpuscular hemoglobin (MCH)	Ery. Mean Corpuscular Hemoglobin
Mean corpuscular volume (MCV)	Ery. Mean Corpuscular Volume
Red blood cell (RBC)	Erythrocytes
Factor VII	Factor VII Activity
Protein C	Factor XIV Activity

Gamma-glutamyl-transferase (GGT)	Gamma Glutamyl Transferase
Globulin	Globulin
Glucose	Glucose
HDL cholesterol	HDL Cholesterol
Human Immunodeficiency Virus (HIV)	HIV Antigen/Antibody
Hematocrit	Hematocrit
Hemoglobin	Hemoglobin
Hepatitis A Virus (HAV)	Hepatitis A Virus Antibody
Hepatitis B Virus (HBV)	Hepatitis B Virus Surface Antigen
Hepatitis C Virus (HCV)	Hepatitis C Virus Antibody
hs-C-Reactive Protein (hs-CRP)	High-sensitivity C-reactive Protein
Indirect Bilirubin	Indirect Bilirubin
IL-6	Interleukin 6
κ FLC	Kappa Light Chain, Free
κ FLC/ λ FLC ratio	Kappa Lt Chain,Free/Lambda Lt Chain,Free
LDL cholesterol	LDL Cholesterol
λ FLC	Lambda Light Chain, Free
White blood cell (WBC)	Leukocytes
Lymphocytes	Lymphocytes
Lymphocytes (%)	Lymphocytes (%)
Monocytes	Monocytes
Monocytes (%)	Monocytes (%)
Neutrophils	Neutrophils
Neutrophils (%)	Neutrophils (%)
Serum Phosphorus	Phosphate
Platelets	Platelets
Potassium	Potassium

Total Protein	Protein
Factor II	Prothrombin Activity
INR	Prothrombin Intl. Normalized Ratio
PT	Prothrombin Time
Sodium	Sodium
Triglycerides	Triglycerides
TNFα	Tumor Necrosis Factor
BUN	Blood Urea Nitrogen
Vitamin A	Vitamin A