DE NOVO CLASSIFICATION REQUEST FOR THERANOVA DIALYZERS (THERANOVA 400, THERANOVA 500)

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Hemodialyzer with expanded solute removal profile. A hemodialyzer with expanded solute removal profile is a device intended for use as part of an artificial kidney system for the treatment of patients with renal failure by performing such therapies as hemodialysis, hemofiltration, and hemodiafiltration. A hemodialyzer with expanded solute removal profile includes modifications to the semipermeable membrane that allows for increased removal of uremic retention solutes compared with standard high-flux hemodialyzers of the high permeability hemodialysis system classification (21 CFR §876.5860), including solutes at the upper end of the "middle" molecular weight range (0.5 kDa to 60 kDa). This device is intended to be used with the extracorporeal hemodialysis delivery systems, blood tubing sets, blood access devices, and accessories regulated under 21 CFR §876.5820, 21 CFR §876.5860, 21 CFR §876.5540, and/or 21 CFR §876.5600.

NEW REGULATION NUMBER: 21 CFR 876.5862

CLASSIFICATION: Class II

PRODUCT CODE: QAX

BACKGROUND

DEVICE NAME: Theranova Dialyzers (Theranova 400, Theranova 500)

SUBMISSION NUMBER: DEN190042

DATE DE NOVO RECEIVED: September 16, 2019

SPONSOR INFORMATION:

Baxter Healthcare Corporation
32650 North Wilson Road
Round Lake, Illinois 60073

INDICATIONS FOR USE

Indications for Use: The Theranova Dialyzer is indicated for patients with chronic kidney failure who are prescribed intermittent hemodialysis. It provides an expanded solute removal profile with increased removal of various middle molecules (up to 45 kDa) that may play a pathologic role in the uremic clinical syndrome. The Theranova

Dialyzer is not intended for hemofiltration or hemodiafiltration therapy. The total extracorporeal blood volume for the Theranova Dialyzer and the set should represent less than 10% of the patient's blood volume.

LIMITATIONS

Theranova Dialyzers are not intended for hemofiltration and hemodiafiltration.

Expanded removal of molecules up to 45 kDa may lead to increased removal of certain drugs. Clinicians should consider this when prescribing the device and make any necessary dosing adjustments.

Expanded removal of molecules up to 45 kDa may lead to increased removal of essential proteins in this size range. Clinicians should consider this possibility when prescribing the device for expanded solute removal.

Water and dialysate should comply with quality standards such as ANSI/AAMI RD62 and ISO 23500. Failure to monitor and maintain water and dialysate quality may result in patient exposure to levels of bacterial or endotoxin contamination capable of causing infection and/or pyrogenic reactions.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Theranova 400 and 500 Dialyzers (referred to collectively as Theranova Dialyzers) are hollow fibers dialyzers that are intended for use in the treatment of chronic renal failure by intermittent hemodialysis. The hollow fiber membrane used in this device is a blend of polyarylethersulfone (PAES) and polyvinylpyrrolidone (PVP). The membrane surface area for the Theranova 400 Dialyzer is 1.7 m^2, while that for the Theranova 500 Dialyzer is 2.0 m^2. Theranova Dialyzers are intended to be used as part of a high permeability hemodialysis system (such as those regulated under 21 CFR §876.5860). Theranova Dialyzers should be used with blood tubing sets with connectors that comply with ISO 8637 and a monitor that controls and monitors the ultrafiltration rate. Theranova Dialyzers are not intended to be used for hemofiltration or hemodiafiltration. They are steam-sterilized, single use only devices.

Theranova Dialyzers are intended to treat chronic renal failure by removal of solutes and plasma water from the blood when used with a hemodialysis monitor capable of ultrafiltration control. The blood travels through the hollow fibers and exits via a blood exit port. Plasma water and certain low and middle molecular weight solutes pass through the hollow fiber membrane and into the countercurrent flowing dialysis solution, removing uremic toxins and waste products by means of diffusion and convection. In addition to the typical removal of small solutes and plasma water, Theranova Dialyzers can remove greater amounts of larger solutes (up to 45 kDa) due to the membrane design.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

Theranova 400 and 500 Dialyzers have direct contact with circulating blood. Although each dialyzer will be used only for a single hemodialysis treatment, hemodialysis patients may receive treatment multiple times per week for several years, with a cumulative contact duration of >30 days.

The Theranova Dialyzers were subject to biocompatibility testing conducted per ISO 10993, FDA guidance document "Use of International Standard, ISO 10993-1 "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process," and

established protocols. The following biocompatibility testing was performed in support of the safety of the Theranova Dialyzers:

- Cytotoxicity
- Senistization
- Intracutaneous irritation
- Material mediated pyrogenicity
- Acute systemic toxicity
- Sub-chronic toxicity
- Hemolysis, direct and indirect
- Complement activation, Sc5b-9
- Coagulation assay, thrombin-antithrombin complex
- In vitro test, beta-thromboglobulin
- Complete blood count
- Genotoxicity, Ames test
- Genotoxicity, chromosome aberration assay
- Chemical characterization

A toxicological risk assessment was performed in addition to the above testing.

PERFORMANCE TESTING - BENCH

Performance testing for Theranova Dialyzers was conducted in conformance with ISO 8637-1, "Extracorporeal systems for blood purification - Part 1: Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators," and to meet the recommendations outlined in FDA Guidance document "Guidance on the Content Premarket Notifications for Conventional and High Permeability Hemodialyzers (August 1998)."

Table 1. Bench Performance Testing

Test	Method	Acceptance Criteria	Results
Ultrafiltration Coefficient	Testing performed according to ISO 8637:2010	N/A; device performance characteristic	Mean ultrafiltration coefficient values [mL/h/mmHg]: Theranova 400: 48 Theranova 500: 59
Pressure drop—blood compartment	Testing performed according to ISO 8637:2010	N/A; device performance characteristic	See Table 2 below
Pressure drop—dialysate compartment	Testing performed according to ISO 8637:2004	N/A; device performance characteristic	See Table 2 below

Clearance of urea	Testing performed according to ISO 8637	N/A; device performance characteristic	See Table 3 below
Clearance of phosphate	Testing performed according to ISO 8637	N/A; device performance characteristic	See Table 3 below
Clearance of creatinine	Testing performed according to ISO 8637	N/A; device performance characteristic	See Table 3 below
Clearance of Vitamin B12	Testing performed according to ISO 8637	N/A; device performance characteristic	See Table 3 below
Clearance of inulin	Testing performed according to ISO 8637	N/A; device performance characteristic	See Table 3 below
Clearance of cytochrome C (marker molecule)	Testing performed according to ISO 8637	N/A; device performance characteristic	See Table 3 below
Clearance of myoglobin	Testing performed according to ISO 8637	N/A; device performance characteristic	See Table 3 below
Clearance of Chitinase-3-like protein 1 YKL-40	Testing performed according to established protocols	Mean clearance of YKL-40 is ≥ 22 mL/min (± 20 %)	Pass for all test articles Mean clearance value [mL/min; @UF = 10 mL/min]: Theranova 400 and 500 Q_B/ Q_D 400/700 mL/min = 30
Sieving coefficient of Chitinase-3-like protein 1 YKL-40	Testing performed according to ISO 8637	Sieving coefficient of YKL-40 ≥30% (± 20%)	Pass
Protein Loss Test	Testing performed according to established protocols	In-vitro protein loss ≤1.13 g/L	Pass
Endotoxin retention testing	Testing performed according to established protocols	Patient exposure to endotoxin is below 5 EU/kg/hr	Pass
Drug removal testing	Testing performed according to established protocols	N/A; comparative testing of device drug removal to other high-flux dialyzers	Representative drugs were not removed significantly differently by Theranova Dialyzers as compared to other high-flux dialyzers

Mechanical hemolysis testing	Testing performed according to established protocols	NA; comparative testing of mechanical hemolysis testing to other high-flux dialyzers	Results establish that Theranova Dialyzers are comparable to other high-flux dialyzers with respect to mechanical hemolysis.

Table 2. Pressure Drop Results

Blood Compartment Pressure Drop [mmHg]

Q_B [mL/min]	Theranova 400	Theranova 500
200	≤ 90	≤ 80
300	≤ 130	≤ 120
400	≤ 170	≤ 160
500	≤ 210	≤ 200
600	≤ 250	≤ 240

Dialysate Compartment Pressure Drop [mmHg]

Q_D [mL/min]	Theranova 400	Theranova 500
300	≤ 20	≤ 15
500	≤ 30	≤ 25
800	≤ 50	≤ 40

Table 3: Clearance Results

Theranova 400 Clearances [mL/min]

UF = 0 mL/min	Q_D = 300 mL/min				
Q_B (mL/min)	200	300	400	500	600
Urea	191	246	272	285	291
Phosphate	179	225	250	266	276
Creatinine	184	232	258	273	282
Vitamin B12	148	178	199	214	226
Inulin	119	140	156	169	180
Cytochrome C	109	128	142	153	164
Myoglobin	93	108	119	129	138

UF = 0 mL/min	Q_D = 500 mL/min				
Q_B (mL/min)	200	300	400	500	600
Urea	198	282	344	388	418
Phosphate	192	261	311	348	376
Creatinine	194	269	323	362	391
Vitamin B12	164	207	239	264	285
Inulin	133	161	183	200	216
Cytochrome C	122	146	165	180	194
Myoglobin	104	123	137	150	161

UF = 0 mL/min	Q_D = 800 mL/min				
Q_B (mL/min)	200	300	400	500	600
Urea	199	293	376	445	502
Phosphate	196	279	345	400	446
Creatinine	198	285	357	416	465
Vitamin B12	174	227	267	301	329
Inulin	144	178	204	225	245
Cytochrome C	133	161	183	202	219
Myoglobin	114	135	152	166	180

Theranova 500 Clearances [mL/min]

UF = 0 mL/min	Q_D = 300 mL/min				
Q_B (mL/min)	200	300	400	500	600
Urea	192	250	276	288	294
Phosphate	182	230	256	271	281
Creatinine	186	237	263	278	286
Vitamin B12	152	185	206	222	235
Inulin	124	147	164	178	189
Cytochrome C	114	134	150	162	173
Myoglobin	98	114	127	138	148

UF = 0 mL/min	Q_D = 500 mL/min				
Q_B (mL/min)	200	300	400	500	600
Urea	199	285	351	397	428
Phosphate	194	267	320	358	388
Creatinine	196	274	331	372	402
Vitamin B12	169	215	249	277	299
Inulin	139	170	193	213	230
Cytochrome C	128	155	175	192	208
Myoglobin	110	130	147	161	173

UF = 0 mL/min	Q_D = 800 mL/min				
Q_B (mL/min)	200	300	400	500	600
Urea	200	295	381	454	515
Phosphate	197	283	354	413	462
Creatinine	199	288	365	428	481
Vitamin B12	178	236	280	317	348
Inulin	150	188	216	241	262
Cytochrome C	139	171	196	217	236
Myoglobin	120	144	163	180	195

**Q_B = blood flow rate, Q_D = dialysate flow rate, UF = ultrafiltration rate*

SHELF LIFE/STERILITY/MICROBIOLOGY

Theranova Dialyzers are steam-sterilized, single use devices tested for both sterility and pyrogenicity. The sterilization method was validated to yield products with a sterility assurance level (SAL) of 10^{-6}. The cycle was qualified using the full cycle overkill approach according to ISO 17665-1:2006.

The finished device is packaged in a peel pouch. The ability of the Theranova Dialyzer packaging to maintain sterility has been confirmed by real-time aging studies.

The product shelf life of three years was supported with testing on steam-sterilized product aged three years, including visual inspection, bubble emission, dye penetration, and peel force testing.

Additionally, packaged Theranova Dialyzers were subject to shelf-life performance tests, performed according to ISO 8637-1, USP <61>, and established protocols. The following tests were conducted in support of the shelf-life of packaged Theranova Dialyzers:

- Structural integrity, positive and negative pressure
- Blood compartment integrity
- Endotoxin, Limulus amebocyte lysate (LAL)
- Bioburden
- Bioburden recovery efficiency
- Bacteriostatis/fungistatis
- Package and label integrity
- Extraction profile via high-performance liquid chromatography (HPLC)
- Urea clearance
- Ultrafiltration coefficient
- Protein loss
- Cytochrome C clearance
- Visual inspection

SUMMARY OF CLINICAL INFORMATION

Theranova 400 Randomized Controlled Trial [NCT03257410]

Study Abstract

A randomized, controlled, open-label trial was conducted in (b) (4) centers in the US to evaluate the efficacy and safety of the Theranova Dialyzer in the context of an expanded solute removal profile compared with Elisio-17H, a similar sized high-flux dialyzer in patients with end-stage renal disease (ESRD). The primary safety endpoint was the pre-dialysis serum albumin level after 24 weeks of treatment. The primary efficacy endpoint was the reduction ratio of lambda free light chains (λFLC) at 24 weeks of treatment. Secondary endpoints included the reduction ratio of other middle to large molecules. A total of (b) (4) clinically stable maintenance hemodialysis patients were randomized to receive thrice weekly in-center dialysis with

Theranova 400 or Elisio-17H over 24 weeks of treatment. Mean age was 59 ± 13 years, 39% were men, 40% Black/African American, and mean dialysis vintage was 5 ± 4 years. Of 86 patients randomized to each dialyzer, 65 completed the trial in each group. The reduction ratio for the removal of λ FLC was significantly higher in the Theranova group compared to the Elisio-17H group after 4 weeks and 24 weeks. Pre-dialysis serum albumin levels were similar between groups after 24 weeks, consistent with non-inferiority of the Theranova Dialyzer in maintaining pre-dialysis serum albumin levels. Among secondary endpoints, the Theranova Dialyzer demonstrated significantly larger reduction ratios at 4 and 24 weeks for complement factor D (CFD), kappa (κ) free light chains, but not for interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα), or Beta 2-microglobulin (β2m). There were no differences in adverse events between the two groups.

Study Objectives

Primary Objectives
The primary efficacy objective of the study was to demonstrate that the Theranova 400 Dialyzer has performance superiority to the Elisio-17H dialyzer in removing lambda immunoglobulin free light chains (λFLCs, 45 kDa).

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

Secondary Objectives
The secondary objectives of the study were 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 monthly trends in pre-dialysis serum albumin levels.

Study design
This was a randomized, controlled, open-label, prospective, multicenter, pivotal clinical trial consisting of (b) (4) subjects at (b) (4) U.S. sites. The controls in this study consisted of subjects treated with the Elisio-17H, a high-flux dialyzer with a similar membrane surface area. Patients were randomly assigned to receive one of the two study dialyzers in a 1:1 ratio according to a central randomization scheme. Randomization was stratified by site and dynamic allocation was used.

Study Endpoints

Primary Endpoints
The primary efficacy endpoint was the pre- versus post-dialysis Reduction Ratio (RR) of λFLC after 24 weeks of treatment.

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

Secondary Endpoints
Secondary efficacy endpoints included:

- Pre- versus post-dialysis reduction ratio of λFLC measured on the first day of treatment and after 4 weeks of treatment.
- Pre- versus post-dialysis reduction ratio of CFD (MW = 27 kDa), κFLC (MW = 23 kDa), IL-6 (MW = 25 kDa), TNFα (MW = 51 kDa), and β2m (MW = 11.6 kDa) measured after 4 weeks and after 24 weeks of treatment.
- Change in pre-dialysis β2m measured on the first day of treatment and after 24 weeks of treatment.
- Urea Clearance (Kt/Vurea) measured after every 4 weeks of treatment.

Secondary safety endpoints included:

- 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; normalized protein nitrogen appearance (nPNA), also known as protein catabolic rate (nPCR), calculated after every 4 weeks of treatment.
- Change from baseline to final measure in chemistry, hematology, and coagulation laboratory tests
- Monitoring of adverse events (AEs), serious adverse events (SAEs)

Exploratory assessments included:

- 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.
- Kidney Disease Quality of Life (KDQOL)-36 measured on the first day of treatment, after 12 weeks and after 24 weeks of treatment.
- EuroQol (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 and phosphate).

Enrollment Criteria

Inclusion Criteria

Each patient had to meet the following criteria to be eligible for the study:

1. ESRD patients age 22 years 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 a 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 [AV] fistula, graft, or dual-lumen tunneled catheter); stable access will be confirmed by observed Kt/V ≥ 1.2 for the past 2 measurements and/or achievement of within 15% the prescribed blood flow rate over 3 treatments prior to study entry.

Exclusion Criteria

Patients who met any of the following criteria were excluded from the study:

1. Are female and pregnant, lactating, or planning to become pregnant during the study period. Note: Female patients of childbearing potential, defined as women < 55 years old who have not had a partial or full hysterectomy or oophorectomy, must have a negative serum beta human chorionic gonadotropin (β -hCG) pregnancy test at screening. Patients 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 /λFLC ratio that is less than 0.37, or greater than 3.1.
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 peritoneal dialysis (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 hemodialysis (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.

Treatments Administered

All randomized patients were to receive dialysis treatments with either the Theranova 400 Dialyzer or the Elisio-17H dialyzer, 3 times weekly for a period of 24 weeks. Trained HD staff administered all treatments. Each patient was to receive 73 treatments during the 24-week study period. Treatment compliance was assessed by counting the number of scheduled treatments delivered to each patient within the study period. A patient might have been withdrawn from the study if more than three consecutive treatments with the randomized dialyzer/treatment mode were missed.

Clinical Assessments

Please see Table 3 below for the schedule of clinical assessments:

Table 3. Schedule of Events

		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	Screening Visit 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 were performed during the mid-week treatment.

[a] Weight was measured at screening and end of study, height was measured only at screening.

[b] Eligible patients were randomized at the end of the Screening Period.

[c] AEs, SAEs and PCs were collected after the informed consent was signed and throughout the study, until the end of study visit. ADEs were collected throughout the treatment period.

[d] Medications were collected throughout the study.

[e] Ultrafiltration (UF) was 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 in the protocol.

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

Analysis Populations

The intent-to-treat full analysis set (FAS) included all randomized patients. The per-protocol set (PPS) included all randomized patients who received 24 weeks of treatment with a study dialyzer without missing 3 consecutive study treatments (i.e., missing a full week of dialysis sessions)

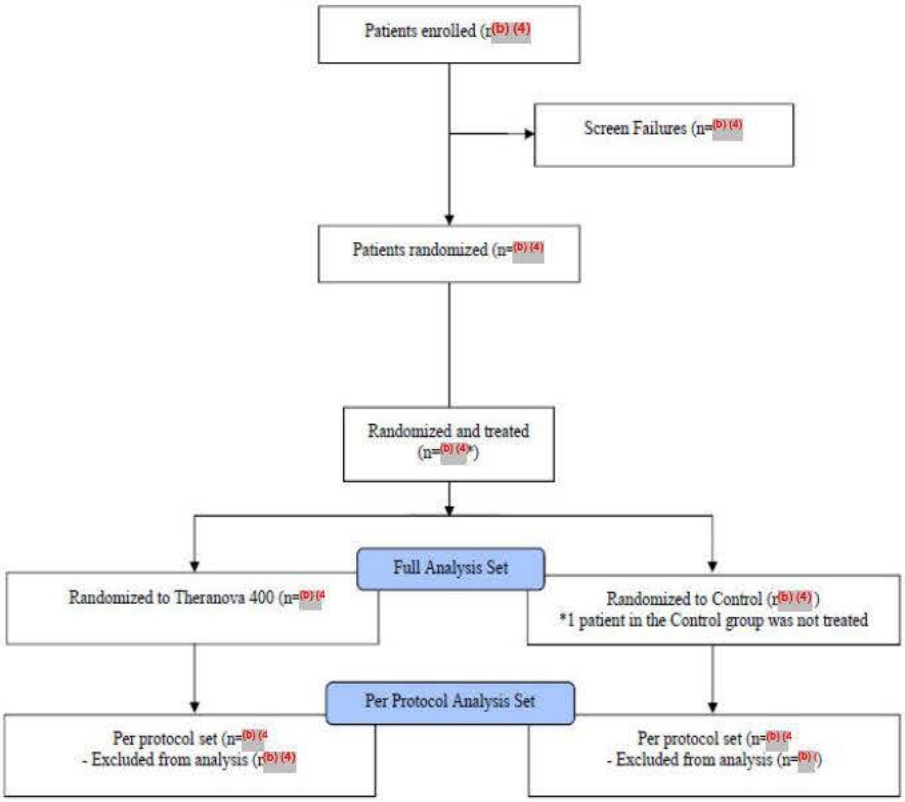
and did not have any major protocol violations that might have impacted the primary analyses. The primary analyses were performed on the FAS and supported by an analysis using the PPS.

Study Results

Disposition of Patients

A total of (b) (4) patients were enrolled in the study and gave informed consent. From these, (b) (4) patients were randomized at (b) (4) sites out of a total of (b) (4) sites. From the enrolled patients, (b) (4) were considered screen failures and were not randomized. Of the (b) (4) patients who were randomized, (b) (4) (50%) were randomized to the Theranova 400 group while (b) (4) (50%) were randomized to the Elisio-17H group, making up the FAS. There were (b) (4) patients who completed the study while (b) (4) (24.4%) patients were withdrawn from the study.

Figure 2. Flowchart of Patient Disposition



The reasons for screen failures, study withdrawal, and exclusion from PPS analysis were reasonable and did not appear to significantly impact study results.

Demographics

The study population are described in the table below:

Table 6. Patient Demographics at Screening (Full Analysis Set)

Characteristics[1]	Value	Theranova 400 (N=(b) (4)	Elisio-17H (N=(b) (4)	Total (N=(b) (4)	*p*-Value
Age (years)	n	(b) (4)			0.5621
	Mean (SD)	58.5 (13.52)	59.7 (12.40)	59.1 (12.95)	
	Median	60.5	60.0	60.0	
	Min, Max	25, 91	22, 86	22, 91	
Sex [n (%)]	Female	32 (37.2%)	35 (40.7%)	67 (39.0%)	0.6390
	Male	54 (62.8%)	51 (59.3%)	105 (61.0%)	

Table 6. Patient Demographics at Screening (Full Analysis Set)

Characteristics[1]	Value	Theranova 400 (N=(b) (4)	Elisio-17H (N=(b) (4)	Total (N=(b) (4)	*p*-Value
Race [n (%)]	American Indian or Alaska Native	0	0	0	0.8363
	Asian	5 (5.8%)	2 (2.3%)	7 (4.1%)	
	Black or African American	33 (38.4%)	35 (40.7%)	68 (39.5%)	
	Native Hawaiian or Other Pacific Islander	3 (3.5%)	3 (3.5%)	6 (3.5%)	
	White	40 (46.5%)	42 (48.8%)	82 (47.7%)	
	Other	5 (5.8%)	4 (4.7%)	9 (5.2%)	
Ethnicity [n (%)]	Hispanic or Latino	19 (22.1%)	23 (26.7%)	42 (24.4%)	0.4815
	Not Hispanic or Latino	67 (77.9%)	62 (72.1%)	129 (75.0%)	
	Not Stated	0	1 (1.2%)	1 (0.6%)	

[1] Listing 16.2.4.1 contains further details on patients' demographics and baseline characteristics.

There was reasonable representation of relevant demographic groups and the two study groups appear to be reasonably balanced.

Medical History

Medical history data were as expected for the study population, given the age range and morbidity of the patients. Commonly reported medical histories in all patients who participated in the study included ESRD, iron deficiency, anemia, hypertension, diabetes mellitus Type 2, secondary hyperparathyroidism, coronary artery disease, malnutrition, and hyperlipidemia. The most common primary renal diagnoses in the FAS (N=(b) (4) included diabetic nephropathy (n=77 [44.8%]), hypertensive nephropathy (n=60 [34.9%]), polycystic kidney disease (n=8 [4.7%]), glomerulonephritis (n=5 [2.9%]), IgA nephropathy (n=3 [1.7%]), and other (n=17 [9.9%]).

Prior and Concomitant Medications
Concomitant medications and non-medication therapies were as expected for the study population, given the age range and morbidity of the patients. Frequently administered medications included those related to kidney disease and anemia such as darbopoetin alfa (Aranesp) and epoetin alfa (Epogen), doxercalciferol (Hectorol), and vitamin B12.

Other Baseline Characteristics
The mean time in years on hemodialysis for the FAS was 5.3 years (Theranova 5.4 years versus Control 4.7 years). There was no significant difference in the type of dialysis between groups (p=0.3676). The type of current vascular access was significantly different between treatment groups (p=0.0439) with more patients in the Theranova group dialyzing with a catheter (7 versus 0%) and fewer dialyzing with AVF (79 versus 86%). The mean blood flow rate in mL/min did not differ significantly between groups (Theranova 400 mean 433.3 mL/min, Control mean 434.0 mL/min; *p*=0.9387), and neither did the dialysate flow rate (Theranova 400 mean 644.7 mL/min, Control mean 655.9 mL/min; *p*=0.4520).

Overall, patient characteristics were similar and representative of the intended population. If anything, the longer dialysis vintage and higher rate of catheter use would favor the control group as worse outcomes are associated with these factors.

Protocol Violations/Deviations
There were a total of (b) (4) major protocol deviations in (b) (4) patients and (b) (4) minor protocol deviations in (b) (4) patients. Three patients in the study groups were withdrawn due to major protocol violations (one patient in the Theranova 400 group, and two patients in the control group; see Table 4). The one patient assigned to Theranova 400 was withdrawn due to having one historical Kt/V value being less than 1.2. In the control group, one patient was withdrawn due to a serious adverse event (SAE), and the other patient was withdrawn due to a randomization error. There were also numerous protocol deviations in which the Theranova study dialyzer was not used in the Theranova group, but these were generally single treatments, during which no data were collected. Sensitivity analyses were performed excluding these treatments and demonstrated findings consistent with the original analyses.

Endpoints
Primary Safety Endpoint:
Theranova 400 Dialyzers were found to be non-inferior to Elisio-17H with regard to pre-dialysis serum albumin levels after 24 weeks of study treatment. In the FAS, the lower bound of the two-sided 95% confidence interval (CI) was -0.098, which met the pre-specified non-inferiority margin (lower bound of the two-sided 95% CI greater than -0.1765 g/dL). In the PPS, the sensitivity analysis on the Observed Data also demonstrated non-inferiority where the lower bound of the two-sided 95% CI was -0.129.

Table 9. Primary Safety Analysis – Pre-dialysis Serum Albumin Assessment of Non-inferiority after 24 Weeks of Treatment Multiple Imputation (Full Analysis Set)

Parameter	Theranova 400 (N=(b) (4)	Elisio-17H (N=(b) (4)	Mean Estimated Treatment Difference (ANCOVA)	Two-sided 95% Confidence Interval[1]
	n Mean (SD) Median Min, Max	n Mean (SD) Median Min, Max		
Pre-dialysis Serum Albumin (g/dL) After 24 Weeks	(b) (4)			
	4.030 (0.2843)	4.018 (0.3935)	-0.015	(-0.098, 0.069)
	4.000	4.000		
	3.16, 4.84	2.39, 4.95		

[1] If the lower bound of the two-sided 95% confidence interval around the mean estimated treatment difference between Theranova 400 and Elisio 17H is > -0.1765 g/dL then non-inferiority can be claimed. If the lower bound of the two-sided 95% confidence interval is > 0, then superiority may be concluded.

Primary Efficacy Endpoint:
Theranova 400 Dialyzers were found to be superior to Elisio-17H with regard to the pre- to post-treatment reduction ratio of λFLC after 24 weeks of study treatment.

Table 7. Primary Efficacy Analysis – Reduction Ratio of λ FLC After 24 Weeks of Treatment Multiple Imputation (Full Analysis Set)

Parameter	Theranova 400 (N=(b) (4)	Elisio-17H (N=(b) (4)	Mean Estimated Treatment Difference (ANCOVA)	Two-sided 95% Confidence Interval[1]
	n Mean (SD) Median Min, Max	n Mean (SD) Median Min, Max		
Reduction Ratio of λ FLC (%)	(b) (4)			
	32.156 (12.6020)	17.514 (12.7235)	14.828	(10.501, 19.156)
	32.610	16.250		
	-33.59, 64.4	-22.55, 74.2		

[1] If the lower bound of the two-sided 95% confidence interval around the difference between Theranova 400 and Elisio-17H is > 0 then superiority will be demonstrated.

Of note, the minimum values in the Table above revealed a negative reduction ratio, which would imply that the levels of lambda FLCs actually increased after therapy. In Supplement S001 to the De Novo submission, the sponsor provided an explanation for this finding, which was likely related to collection or measurement error. Overall, the primary effectiveness endpoint results appear to be robust across analysis populations and sensitivity analyses.

Of note, lambda FLC (45kDa) was agreed upon as the "middle molecule" to be used for the primary effectiveness endpoint in the study. While the involvement of this molecule in the uremic clinical syndrome is debatable, it was considered to be a readily available marker at the higher end of the "middle molecule" size range.

Secondary Endpoints:

(b) (4)

Compared with the Elisio-17H, the Theranova 400 Dialyzers had an increased pre to post-treatment reduction ratio of λFLC, Complement Factor D, and κFLC after 4 and 24 weeks of study treatment. The reduction ratios of IL-6, TNF α , and β2-microglobulin were not significantly different between the two groups.

At Week 24, there was a significant difference in the mean change from baseline of λFLCs between the two groups:

Mean Change from Baseline for Free Light Chains (FLC) at 24 weeks			
	Theranova	Control	p-value
λFLCs (45kDa)	-19.40 mg/L [±31.635]	1.75 mg/L [±29.946]	p=0.0002
κFLCs (23kDa)	-84.81 mg/L [±97.359]	-43.01 mg/L [±75.677]	p=0.0012

There was no significant difference in the mean change from baseline of the other protein parameters (total protein, globulin, Factor II, albumin, Protein C, TNFα, Factor VII, IL-6, CFD, and β2-microglobulin) between the groups. The results for λ and κ FLCs suggest that hemodialysis using Theranova Dialyzers can have a persistent effect (i.e., net removal) on the serum levels of some middle molecules that can accumulate in ESRD.

There was a small, but statistically significant reduction in serum albumin noted at Weeks 4 and 8. However, changes from baseline were not significantly different between the two study groups at Week 12 and thereafter. There was also no significant difference in the mean change from baseline for pre-dialysis level of: Factor VII, Protein C and Factor II after 12 weeks and after 24 weeks of treatment; Vitamin A after 4 weeks and 24 weeks of treatment; and nPNA after each 4 weeks of treatment (Week 4, 8, 12, 16, 20, and 24).

There were some small, but significantly different changes in electrolytes from baseline:

Mean Electrolyte Laboratory Changes from Baseline to End of Study			
	Theranova	Control	p-value
Calcium	-0.06 mmol/L [±0.154]	-0.02 mmol/L [±0.151]	p=0.0340
Potassium	0.08 mmol/L [±0.727]	-0.23 mmol/L [±0.665]	p=0.0058
Phosphate	-0.03 mmol/L [±0.438]	-0.19 mmol/L [±0.500]	p=0.0285
Glucose	-0.20 mmol/L [±2.197]	-0.47 mmol/L [±2.858]	p=0.0125

Despite these differences, the mean levels of calcium, potassium, phosphate and glucose remained within the normal range for these substances. Thus, the changes were unlikely to be clinically significant. There was no significant difference in the mean change from baseline to End of Study for chloride, sodium, and bicarbonate between the groups.

There were some small, but significantly different changes in hematology laboratory studies from baseline:

Mean Hematology Laboratory Changes from Baseline to End of Study			
	Theranova	Control	p-value
Hematocrit	0.03 L/L [±0.055]	0.01 L/L [±0.042]	p=0.0297
Mean corpuscular volume	4.88 fL [±5.371]	1.93 fL [±4.778]	p=0.0067
WBC	-0.22 109/L [±1.640]	0.49 109/L [±2.464]	p=0.0463
Platelets	-8.65 109/L [±41.711]	7.99 109/L [±49.215]	p=0.0434

Despite these significant differences, for both groups, the WBC and platelets values were still within the normal range and the hematocrit levels were within the expected range for hemodialysis patients. Thus, the changes were unlikely to be clinically significant. There was no significant difference in the mean change from baseline to end of study for hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cells (RBC), basophils, eosinophils, lymphocytes, monocytes and neutrophils.

There was no significant difference in the mean change from baseline to End of Study for the coagulation parameters (Prothrombin Time, mean International Normalized Ratio, and mean Activated Partial Thromboplastin Time).

There was no significant difference in the mean change from baseline to after 24 weeks treatment for pre-dialysis BUN, post-dialysis BUN, BUN reduction ratio, and in the mean change from baseline to End of Study for creatinine between the groups. There was also no significant change in Kt/V (urea) between the two study groups over the course of the study.

There was no significant difference in the mean change from baseline of Vitamin A, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides between the groups. There was also no significant difference in the mean change from baseline to End of Study for the liver function parameters between the groups.

No significant differences were observed between the Theranova and the control groups in incidence (p=0.87) and incidence rate (p=0.59) of adverse events (AEs). There was also no statistically significant difference in the number of serious adverse events (SAEs) or device-related AE between the two groups. No SAEs were considered to be device-related. Six patients died during the study, 3 in each group. None of the deaths were considered to be related to the investigational device or the hemodialysis treatment.

None of the AEs were unanticipated, and they were largely the AEs typically seen in maintenance HD patients. Analysis of AEs by MedDRA System Organ Class (SOC) and MedDRA preferred term (PT) did not reveal any significant differences when comparing Theranova to Control. Overall, the most frequent AEs by PT for Theranova were nausea, cough, viral upper respiratory infection (URI), fall, and infusion site extravasation. The more frequent AE by PT for the control group were procedural hypotension, fluid overload, hyperkalemia, diarrhea, muscle spasm, and pruritus. There were six total device-related (probably or possibly

associated) AEs by PT. These included two episodes of pruritus for Theranova and 4 separate AEs (inadequate hemodialysis, muscle spasms, dizziness, pruritus) for the control group. There were a few notable trends, including a higher proportion of pyrexia events in the Theranova group (3.49 vs. 0%). FDA requested additional information related to the pyrexia events (3 subjects, 4 total events, 2 considered serious) given the risk of backfiltration of endotoxin across the membrane with larger pore sizes. However, upon review of the subject-level data (provided by the sponsor) for these AEs, it seemed unlikely that the fevers noted during the study were related to the backfiltration of endotoxin based on the timing of fevers, water quality data, etc. There were also higher proportions of subjects with nausea (6.98 vs. 1.18%), viral URI (4.65 vs 2.35%), headache (3.49 vs. 1.18%), and cough (6.98 vs. 3.53), but these differences were not statistically different and were of unclear clinical significance.

Exploratory Assessments
There were no significant differences between the two groups for high-sensitivity C-Reactive protein (hs-CRP), changes in utilization for medication (i.e., erythropoiesis-stimulating agent (ESA), anti-hypertensives, iron), or patient reported outcomes (KDQOL-36 or EQ-5D-5L).

APPLICABILITY OF CLINICAL STUDY DATA TO THERANOVA 500 DIALYZERS

Compared with Theranova 400 Dialyzers, Theranova 500 Dialyzers have a larger membrane surface area of 2.0 m^2, allowing for increased urea clearance to provide an adequate dialysis dose for larger patients. Although the larger membrane surface area does permit a greater Kt/V for urea, Theranova 500 Dialyzers meet the same albumin removal release specification and endotoxin retention requirement as Theranova 400 Dialyzers. *In vitro* data demonstrated comparable albumin loss with the Theranova 400 (3.1 ± 0.30 grams per 4-hour simulated treatment) and Theranova 500 (2.8 ± 0.54 grams per 4-hour simulated treatment) dialyzers. Additionally, data from an independent clinical study[1] supported that the THERANOVA 400 and 500 Dialyzers had similar quantities of albumin removed *in vivo* during actual hemodialysis treatments (Theranova 400 - 2.35 ± 1.03 g vs. Theranova 500 - 1.89 ± 0.97 g; $p = 0.104$). The same study found no significant difference in the reduction ratios for other measured solutes (β2-microglobulin – 11.8 kDa, myoglobin – 17.2 kDa, prolactin – 23 kDa, α_1 -microglobulin – 33 kDa, and α_1- acid glycoprotein – 41 kDa), supporting that the potential risk of removal of native beneficial molecules is not significantly different between the two sizes of dialyzers. This is also supported by the *in vitro* clearance testing (listed above) that shows equivalent clearance rates for all tested molecules.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

[1] Maduell F, Rodas L, Broseta JJ, et al. Evaluation of the influence of the surface membrane and blood flow in medium «cut-off» (MCO) dialyzers. Valoración de la influencia de la superficie de la membrana y el flujo sanguíneo en dializadores de medio cut-off. *Nefrologia*. 2019;39(6):623-628.

The label affixed to the Theranova device includes:

- Device name
- U.S. point of contact
- Manufacturer's name, address, and phone number
- Storage conditions
- Priming volume
- Sterility status and sterilization method,
- Sterilization date
- Effective membrane surface area
- Lot number
- Expiration date
- An indication whether the device is for single or multiple use

The Theranova device instructions for use includes:

- A statement that includes specific indications and intended patient population
- Contraindications, Warnings, and Precautions relevant for the device, including the following:
    - Warning that they are to be used only with hemodialysis delivery machines with ultrafiltration controllers
    - Warning that expanded removal of molecules up to 45 kDa may lead to increased removal of certain drugs. Clinicians should consider this when prescribing the device and make any necessary dosing adjustments.
    - Warning that expanded removal of molecules up to 45 kDa may lead to increased removal of essential proteins in this size range. Clinicians should consider this possibility when prescribing the device for expanded solute removal.
    - Warning that water and dialysate should comply to quality standards such as ANSI/AAMI RD62 or ISO 23500. Failure to monitor and maintain water and dialysate quality may result in patient exposure to levels of bacteria or endotoxin contamination capable of causing infection and/or pyrogenic reactions.
    - "CAUTION: Federal law restricts this device to sale by or on the order of a physician."
    - CAUTION! Do not apply isolated/sequential ultrafiltration when using Theranova Dialyzers, due to higher permeability for larger plasma proteins such as free hemoglobin. This may lead to a reddish coloration of the ultrafiltrate which may trigger the internal blood leak detector.
- Comprehensive instructions for the preparation of the hemodialyzer, initiation of dialysis, troubleshooting, and discontinuance of dialysis
- A listing of the membrane surface area, priming (blood) volume, maximum transmembrane pressure, maximum blood flow and maximum dialysate rate for each model
- A summary of the *in vitro* performance data, provided in tabular form
- A summary of the clinical performance data.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with the use of hemodialyzers with expanded solute removal profile and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Adverse tissue reaction	Biocompatibility evaluation Pyrogenicity testing Non-clinical performance testing
Infection or pyrogen reaction	Labeling Pyrogenicity testing Sterilization validation Non-clinical performance testing Shelf life testing
Inadequate or incomplete treatment	Non-clinical performance testing Labeling Shelf-life testing
Clearance of essential blood substances or medications	Non-clinical performance testing Clinical performance testing Labeling Shelf-life testing
Blood loss or blood cell destruction	Non-clinical performance testing Labeling Shelf-life testing
Blood leak into the dialysis fluid	Non-clinical performance testing Labeling Shelf-life testing
Air or particle embolism	Non-clinical performance testing Labeling Shelf-life testing
Fluid imbalance	Non-clinical performance testing Labeling
Acid-base imbalance	Non-clinical performance testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the hemodialyzer with expanded solute removal profile is subject to the following special controls:

1) Clinical performance testing under anticipated conditions of use must evaluate the solute removal profile and document all adverse events.
2) Non-clinical performance testing data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:

(A) Ultrafiltration;
(B) Blood and dialysate pressure drop;
(C) Clearance rates;
(D) Sieving coefficients;
(E) Mechanical hemolysis;
(F) Structural integrity;
(G) Blood compartment integrity;
(H) Volume of the blood compartment; and
(I) Endotoxin retention of the dialyzer membrane.

3) The tissue-contacting components of the device must be demonstrated to be biocompatible. Biocompatibility evaluation must include a chemical analysis of the dialyzer membrane.
4) Performance data must demonstrate the sterility of the patient-contacting components of the device.
5) The patient-contacting components of the device must be demonstrated to be non-pyrogenic.
6) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.
7) Device labeling must include:
   (A) Shelf life;
   (B) Storage conditions;
   (C) Instructions for the preparation of the hemodialyzer, initiation of dialysis, troubleshooting, and discontinuance of dialysis;
   (D) Membrane surface area, priming (blood) volume, maximum transmembrane pressure, maximum blood flow and maximum dialysate rate for each model;
   (E) A non-pyrogenic statement;
   (F) A summary of the *in vitro* performance data, provided in tabular form; and
   (G) A summary of the clinical performance data.

BENEFIT-RISK DETERMINATION

Benefits

The benefits of the device over existing technology primarily include the ability to clear molecules from the circulation that represent the larger (up to 45kDa) uremic toxins that are normally cleared by the kidney but accumulate in patients with End-Stage Renal Disease. As there is currently a limited understanding of which particular uremic toxin molecules should be targeted for removal, the sponsor evaluated "marker" molecules in the size range that would normally be removed by the native kidneys, but not by conventional dialysis therapy. Compared to a conventional high-flux dialyzer, the proposed device demonstrated an increased reduction ratio (difference between pre- and post-treatment in a single treatment) for the following molecules:

- Lambda FLC (45kDa)
- Complement Factor D (28kDa)
- Kappa FLC (22.5kDa)

Additionally, the sponsor demonstrated serial reduction in pre-dialysis levels after 24 weeks of treatment:

- Lambda FLC (45kDa)
- Kappa FLC (22.5kDa)

Thus, in addition to greater removal during treatment, there was also an overall net removal over time for these molecules that can accumulate in ESRD.

This device may address an unmet need given that it removes larger molecules (including potential uremic toxins) not removed by conventional hemodialysis. There is some uncertainty related to which specific molecules should be removed and which are clinically associated with the uremic syndrome, but this uncertainty has always existed in this clinical area. Even urea, on which "uremia" has been classically defined, has questionable pathophysiologic significance. In this submission, uremic toxin surrogates were chosen largely based on their molecular size. Also, while the randomized population was reasonably representative of the ESRD population, there is additional uncertainty related to the 24.4% early withdrawal rate. The rate was the same for both Theranova and Control, and the reasons for withdrawal were largely consistent with other studies for ESRD population. There is also uncertainty related to the number of protocol deviations ((b) (4) major, (b) (4) minor). Deviation types were reasonably similar between the two groups and w re thought to have a minimal impact on the efficacy results.

Risks

Given the design differences compared with conventional hemodialyzers, the primary focus of the benefit-risk analysis is on the areas of possible increased risk with the proposed device. As noted by the sponsor, these are primarily related to the larger pore size and include:

- albumin removal
- beneficial molecule removal
- infection/pyrogenicity

In the study, the sponsor demonstrated no difference (within the prespecified noninferiority margin) in albumin levels at 24 weeks of therapy compared with a conventional high-flux dialyzer. There was a statistically significant reduction in serum albumin levels after 4 and 8 weeks of treatment, but levels rebounded over time. The clinical significance of a temporary reduction like this is unclear. Given that the clinical study only used the Theranova 400 device, there is some uncertainty related to whether there would be increased albumin removal with the larger surface area Theranova 500 device. However, the sponsor provided additional *in vitro* and clinical data to help address this uncertainty. FDA believes that this risk has been adequately mitigated with bench testing, clinical testing and labeling.

For beneficial molecule removal, the sponsor conducted bench performance testing to characterize the solute removal characteristics of the membrane. They also performed drug removal testing to compare relative removal of representative drugs compared with standard high-flux dialyzers. In the clinical study, the sponsor evaluated a range of beneficial molecules of different sizes. Of the molecules studied, there was no clinically or statistically significant reduction over the course of 24 weeks of therapy. Additionally, there were no notable signals in the overall adverse events that would imply a device-related deficiency of beneficial molecules. Given that the clinical study only used the Theranova 400 device, there is some uncertainty

related to whether there would be increased beneficial molecule removal with the larger surface area Theranova 500 device. However, the sponsor provide additional *in vitro* and clinical data to help address this uncertainty. FDA believes that this risk has been adequately mitigated with bench testing, clinical testing and labeling.

Regarding infection/pyrogenicity, the sponsor provided in vitro testing to demonstrate that despite the larger pore size, endotoxin would not pass into the bloodstream from the dialysate side, even under worst case conditions. There was a small but increased frequency of reported pyrexia in the Theranova group that FDA thought could suggest an increased risk of pyrogen reaction from the backfiltration of endotoxin. However, the sponsor provided additional information/data for these patients/sites that demonstrated that these fever episodes were not likely related to pyrogen reactions from backfiltration of endotoxin. Thus, FDA believes that this risk is adequately mitigated with performance testing and labeling.

Outside of the risks related to the larger pore size, the majority of potential device risks are shared with conventional high-flux hemodialyzers (acid-base imbalance, air embolism, blood loss, chemical injury, hemolysis, hypovolemia, infection, mechanical injury, particle embolism, patient reactions, fluid overload, inadequate dialysis, hypotension). This notion is supported by the data from the clinical study, in which there were no significant differences in total AEs, SAEs or device-related AEs between the Theranova and the control groups. Additionally, none of the AEs were unanticipated and were largely AEs that are typically seen in maintenance HD patients. It is important to note that uncertainty exists in interpreting the risks observed during clinical trial conditions, especially given the early withdrawal rate and observed protocol deviations. However, these were balanced across the two groups and largely consistent with other studies for the ESRD population.

PATIENT PERSPECTIVES

The clinical study evaluated two patient reported outcome measures (KDQOL-36 or EQ-5D-5L). There were no significant differences in these measures between the two groups.

BENEFIT/RISK CONCLUSION

The sponsor has demonstrated the ability to remove middle molecules (up to 45 kDa) that may be involved in the pathology of the uremic clinical syndrome. This may address an unmet need given that these larger molecules are not removed by conventional hemodialysis. The main uncertainty for this benefit is that sized-based surrogate markers for uremic toxins were used. The main risks include removal of essential/beneficial molecules/proteins. However, the clinical study did not demonstrate a clinically significant change in albumin levels or levels of the other essential proteins that were measured. There is some uncertainty in that it was not feasible to measure all proteins. However, there were no trends in adverse effects that would suggest clinically relevant removal of essential molecules. Otherwise, the risks seen with this device were consistent with known risks for conventional high-flux hemodialyzers used during hemodialysis treatments. It is also important to note that the device would likely be a life-long therapy, but the study only evaluated outcomes out to 6 months. Thus, there also remains some uncertainty about the benefits and risk with longer-term use.

In conclusion, given the available information above, the data support that for the stated indications for use, the probable benefits outweigh the probable risks for the Theranova Dialyzers. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Theranova Dialyzers (Theranova 400, Theranova 500) is granted and the device is classified as follows:

Product Code: QAX
Device Type: Hemodialyzer with expanded solute removal profile
Regulation Number: 21 CFR 876.5862
Class: II