FRESENIUS MEDICAL CARE
RENAL THERAPIES GROUP (RTG), LLC

TITLE:	A Randomized, Open Label, Cross-over Feasibility Study for Heparin-free Hemodialysis with the Dialyzer with Endexo™ in End-Stage Renal Disease (ESRD)Subjects
PROTOCOL NUMBER:	Endexo-002
INVESTIGATIONAL PRODUCTS (IP):	Dialyzer with Endexo™, Fresenius Medical Care North America
SPONSOR:	Fresenius Medical Care RTG, LLC Medical Department, Clinical Research 920 Winter Street Waltham, MA 02451–1457
ORIGINAL PROTOCOL:	Version 1.0 [11AUG2020] NCT04511338

PROTOCOL SYNOPSIS

Title	A Randomized, Open label, Cross-over Feasibility Study for Heparin-free Hemodialysis with the Dialyzer with Endexo™ in End-Stage Renal Disease (ESRD) Subjects
Protocol Number	Endexo-002
Study Type	Feasibility study
Investigational Product (IP)	Dialyzer with Endexo, Fresenius Medical Care North America
Proposed Indication	The dialyzer with Endexo used with either the CombiSet® bloodline[1] or the Streamline® bloodline[2], and Citrasate® dialysate are intended for heparin-free hemodialysis treatments of patients with acute or chronic renal failure when conservative therapy is judged to be inadequate. The dialyzers with Endexo must be used in conjunction with dialysis machines equipped with ultrafiltration control and are to be used only as directed by a physician. [1] *Fresenius Medical Care North America* [2] *B. Braun Medical Inc.*
Study Objective(s)	The primary objective of this study is to explore the feasibility of heparin-free hemodialysis (HFHD) with two extracorporeal dialysis circuits (A, B) in ESRD subjects maintained on conventional hemodialysis (HD) with Citrasate dialysate and regularly prescribed heparin. Circuit (A): dialyzer with Endexo and CombiSet bloodline Circuit (B): dialyzer with Endexo and Streamline bloodline The secondary objective is to collect and summarize adverse events with both dialysis circuits.
Study Design	This is a randomized, open-label, cross-over study with subjects on thrice-weekly (in-center) hemodialysis. The study consists of a Screening Period, two Study Periods (1 and 2), a Washout Period and a Follow-up Visit. A study design diagram is presented in Appendix I. After screening, chronic kidney disease subjects on thrice weekly conventional HD with Optiflux dialyzer (F160NR and F180NR), standard of care (SOC) bloodline, Citrasate dialysate, and regularly prescribed heparin dose will be assigned randomly to one of the treatment sequences: AB or BA. • Circuit (A) includes the dialyzer with Endexo and the CombiSet bloodline. • Circuit (B) includes dialyzer with Endexo and the Streamline bloodline Each sequence includes two study periods (Period 1 and Period 2) and a Washout period. • Period 1 and Period 2 consist of 5 HD sessions per period (5 Visits per period): The 1st HD session with the regularly prescribed Heparin dose, the 2nd HD

session with 50% of the prescribed Heparin dose, and the 3rd, 4th and 5th HD sessions with 0% Heparin (heparin-free).

- The Washout period is performed between Period 1 and Period 2. It consists of 3 conventional HD sessions (3 Visits).

The tables below provide a summary for study periods and HD visits:

Table 1: Summary of Study Periods

Randomization	Period 1 (Five Visits: 1,2,3,4,5)	Washout Period*** (Three Visits: 6,7,8)	Period 2 (Five Visits: 9,10,11,12,13)
Sequence AB	A*		B**
Sequence BA	B**		A*

*Circuit A: dialyzer with Endexo + CombiSet bloodline

**Circuit B: dialyzer with Endexo + Streamline bloodline

***Conventional HD

Table 2: Summary of HD Visits during Periods 1 and 2

Period 1 and Period 2 (Circuit A or B)	
Visit 1 and Visit 9	Regularly prescribed Heparin dose
Visit 2 and Visit 10	50% of the regularly prescribed Heparin dose
Visit 3 and Visit 11	0% Heparin (Heparin-free)
Visit 4 and Visit 12	0% Heparin (Heparin-free)
Visit 5 and Visit 13	0% Heparin (Heparin-free)

Table 3: Summary of the Washout Period

Washout Period	
Visits 6, 7, and 8	Conventional HD

Study Population	The study population will consist of ESRD subjects who are a minimum of 22 years of age and have been prescribed in center thrice weekly HD for at least 180 days prior to the date of signed informed consent.
Total Number of Subjects	12–16 eligible subjects will be enrolled
Total Number of Sites	1–2 (United States)

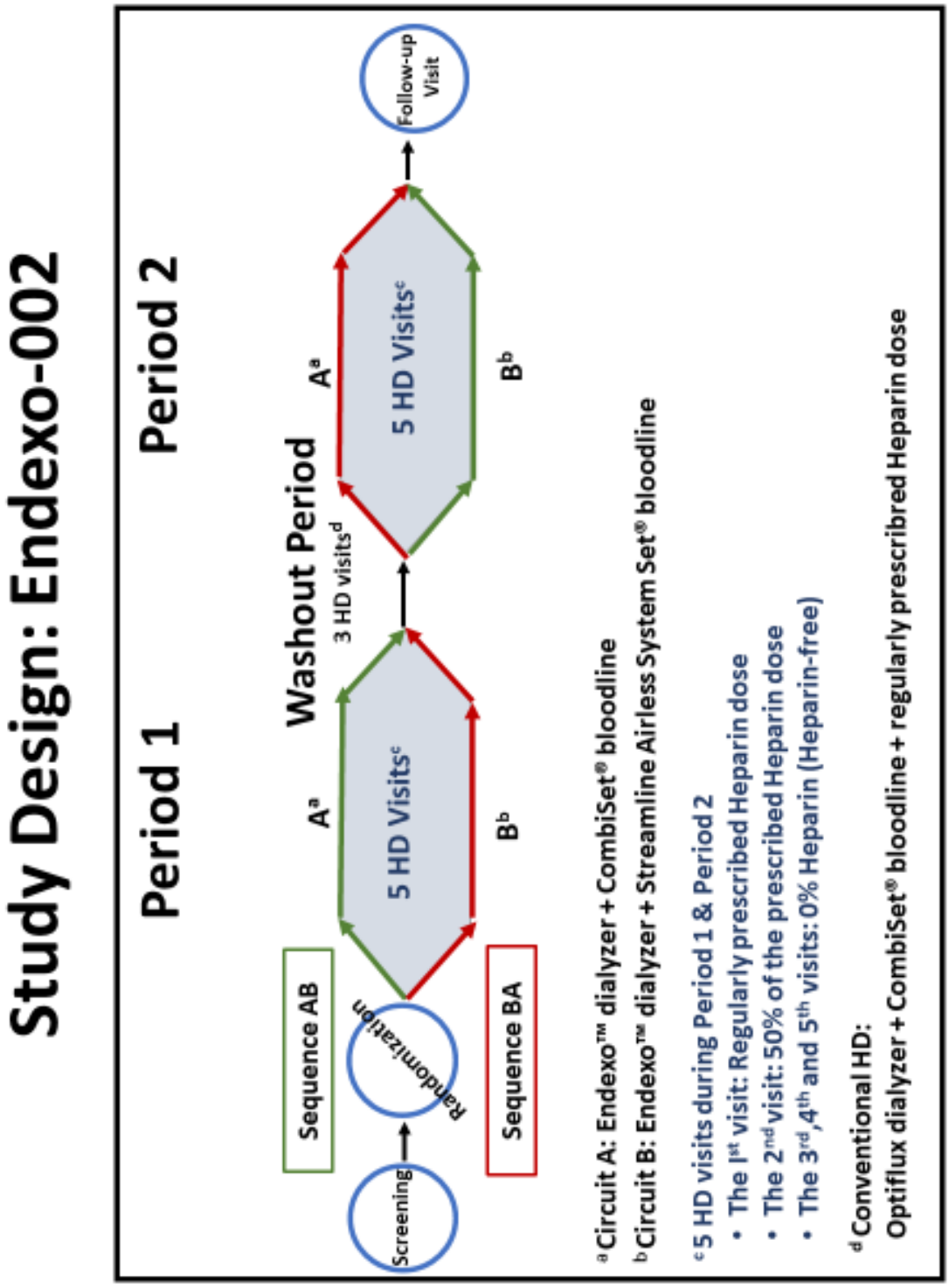
Estimated Duration of Study	Each subject will participate in the study for approximately 10 weeks. • Screening Period up to 4 weeks. • Two Study Periods (Period 1 and Period 2) including 5 HD sessions per period (approximately 2 weeks per subject per period). • A Washout Period includes 3 HD sessions (1 week) between the Study Periods 1 and 2. • A Follow-up Visit within one week of the subject's last study HD session. After the subject's last study HD session, the subject will resume HD as prescribed by his/her physician.
Inclusion Criteria	A subject who signed the ICF must meet all the following inclusion criteria in order to be eligible for enrollment in the study: 1. Must be an adult, defined as having had a 22nd birthday on or before the date of signed informed consent 2. Has been prescribed in center thrice weekly HD for at least 180 days prior to the date of signed informed consent 3. Has been on Conventional HD for at least 30 days prior to the date of signed informed consent. Conventional HD includes: Optiflux dialyzer (F160NR or F180NR), SOC bloodline, Citrasate dialysate, and regularly prescribed heparin dose. 4. Has a prescribed HD treatment duration ≥180 minutes (3 hours) and ≤270 minutes (4.5 hours) at the time of signed informed consent 5. Has a well-established functional permanent vascular access (AVF, AVG) that can allow a blood flow of at least 250 mL/min 6. Has been on a regularly prescribed heparin dose for HD and has had no change in heparin prescription within 14 days prior to the date of signed informed consent 7. Has the following most recently available laboratory results within 45 days prior to the date of signed informed consent: a. Single pool Kt/V (spKt/V) ≥1.2 b. Hemoglobin ≥9 g/dL c. Platelet count ≥100,000/mm^3 8. A female of childbearing potential must have a negative serum pregnancy test at the time of screening and agree to use an acceptable method of contraception during the study
Exclusion Criteria	A subject who signed the ICF is excluded from the study if any of the following criteria are met: 1. Known allergic reactions to Endexo 2. Known heparin contraindications 3. Hospitalization within 30 days prior to the date of signed informed consent 4. Presence of active malignancy, congestive heart failure New York Heart Association (NYHA) Class III or IV (see Appendix III), or liver cirrhosis

	5. Is receiving or has received chemotherapy/radiation therapy/immunotherapy/plasmapheresis therapy within 90 days prior to the date of signed informed consent 6. Is receiving oral or/and intravenous (IV) antibiotics or has used oral or/and IV antibiotics within 14 days prior to the date of signed informed consent 7. Is currently enrolled in or has completed any other investigational product study within 30 days prior to the date of signed informed consent 8. Is receiving anticoagulants including vitamin K antagonists 9. Is receiving a glycoprotein platelet inhibitor 10. Is receiving more than one anti-platelet medication 11. Is receiving systemic heparin therapy for prevention or treatment besides heparin prescribed for dialysis 12. Requiring blood and other labile blood products (for e.g., fresh frozen plasma, platelets) transfusion during HD treatments 13. Has history of clotting or bleeding disorders 14. Has history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the participant's ability to follow the requirements of the study and participate for the full duration of the study, or is not in the best interest of the subjects to participate, in the opinion of the investigator.
Study Endpoints	**Primary endpoint:** • The number and percent (%) of successful heparin-free HD* sessions for each subject in each circuit ***Definition of a successful HD Session:** A successful HD session must meet all the following criteria: 1. Absence of complete HD circuit occlusion (Grade 4) rendering dialysis impossible 2. Absence of the need to replace dialyzers or bloodlines due to clotting 3. Absence of saline flushes to maintain blood flow through the circuit during the HD session 4. Absence of any additional heparin beyond what is allowed per study visits 5. Single pool Kt/V (spKt/V) ≥ 1.2 **Secondary endpoint:** • Adverse events and device-related adverse events **Additional Assessments:** • Number and percentage of dialyzers and bloodlines for each clotting grade using the visual inspection clotting grade scale (Appendix II) • HD treatment duration or time to complete circuit occlusion (Grade 4) • Blood volume processed per dialysis session

	• The volume, the time of saline administered and the reason for administration per subject per HD session (other than for circuit priming or rinse back) • Urea Reduction Ratio (URR) and spKt/V for all HD sessions
Exploratory Assessment	Pictures of the arterial and venous end caps of the dialyzer with Endexo, arterial and venous drip chambers for CombiSet bloodline and venous chambers, arterial and venous pods for Streamline bloodline will be taken by the study sites at the end of each HD session.
Data Collection	The data listed below will be collected in the study: 1. Demographics 2. Medical History, historical laboratory values and Concomitant Medications 3. Physical Exam, Vital Signs, Body Measurements (height, weight) 4. Adverse events, serious adverse events, and device deficiencies 5. HD Treatment parameters: a. Initial HD Prescription b. Data collection during dialysis treatment: ▪ Blood flow rate (Qb), dialysate flow rate (Qd), arterial pressure (AP), venous pressure (VP), at initiation of the HD sessions and every 30 ± 15 minutes ▪ KECN recorded at initiation of the HD sessions and every 30 ± 15 minutes c. HD Treatment Data: ▪ Treatment Time (Td), mean Qb, mean Qd, mean AP and VP, mean ultrafiltration volume and rate, and blood volume processed ▪ Mean KECN d. Volume, time and the reason for saline flushes administration (other than for circuit priming or rinse back) e. HD Treatment-related Medications (total heparin units given [bolus + maintenance]) when applicable f. Duration of blood flow cessation during hemodialysis treatment estimated as the difference between the Ultrafiltration (UF) clock and the Remaining Time on Dialysis (RTD) clock. 6. Thrombus scoring at the end of each HD session: a. Visual thrombus scoring of dialyzer end caps, and bloodline drip chambers and pods will be performed (Grade 1–4) and recorded by site staff (the investigator or a designee). For further details, see Appendix II. b. Digital pictures of the dialyzer end caps, and bloodline drip chambers and pods will be taken by site staff. 7. Laboratory Assessments: a. At screening: ▪ Serum pregnancy test for females of childbearing potential

	b. Periods 1 and 2: ▪ Pre- and post-hemodialysis for Visits (1–5) and (9–13): – Complete Blood Count with differential (CBC with diff), Blood Urea Nitrogen (BUN), and Albumin ▪ Pre- and post-hemodialysis for Visits 1,3, 9 and 11: - β_2 Microglobulin (B2M), C-Reactive Protein (CRP), Interleukin-6 (IL-6) and Ferritin
Sample Size Determination	For this feasibility study, we proposed to enroll 12–16 eligible subjects. The sample size was not calculated based on any estimates or comparisons.
Statistical Methods	Analysis for primary endpoint: The descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for the number and percent of successful heparin-free HD sessions for each circuit. The frequency for subjects with possible successful heparin-free sessions (0, 1, 2, or 3) will be displayed for each circuit. Analysis for secondary endpoints: The number and percent of subjects with adverse events, and the number of adverse events will be presented for each circuit by system organ class and preferred term using MedDRA. The device-related adverse events will be listed for each circuit. Additional assessments: Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented for continuous endpoints for each circuit. Frequency and percent will be presented for categorical endpoints for each circuit.
Safety Monitoring/Safety Oversight	All adverse events (AE) and serious adverse events (SAE) regardless of relatedness to the Investigational Product (IP) will be captured from the time the subject signs the ICF until the subject completes or withdraws from the study. The site investigator must inform the Sponsor of every SAE, within 24 hours of becoming aware of the occurrence. The study medical monitor will evaluate and monitor safety of the subjects during the study. If the Sponsor determines that an unanticipated adverse event or serious adverse event presents an unreasonable risk to the subjects, the Sponsor will terminate the study as soon as possible.

APPENDIX I: Study Design Endexo-002



Appendix II: Clotting scales

During Period 1 and 2, an investigator or designee is to perform thrombus scoring on dialyzer arterial and venous end caps, and bloodline drip chambers and pods at the end of dialyzer/bloodline use. All observers will be trained on the scoring prior to study start. The same observer should perform the evaluations as much as possible throughout the study. After use, the observer is to select one of the 4 possible grades as described in the tables below (The pictures in the tables are for reference only. The observer must assign the grade based on the description, not the pictures).

The following areas of the circuits need to be scored:

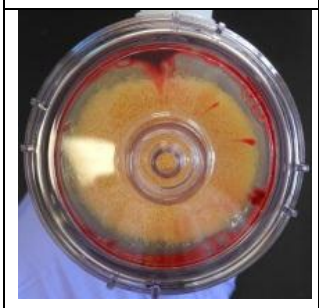
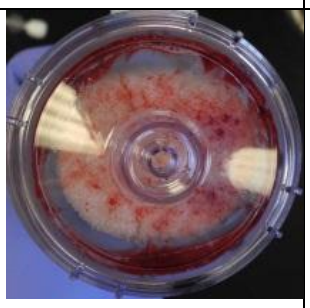
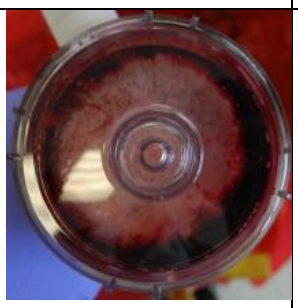
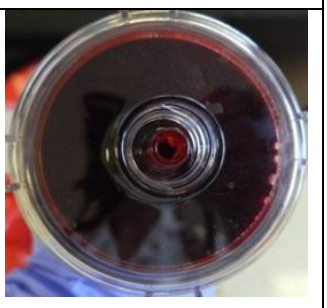
Dialyzer with Endexo: 1) arterial end cap and 2) venous end cap

CombiSet bloodline: 1) arterial chamber and 2) venous chamber

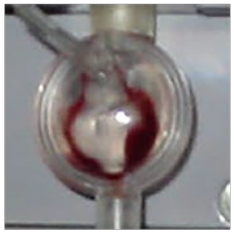
Streamline bloodline: 1) venous Chamber, 2) arterial pod and 3) venous pod

a) Dialyzer arterial and venous end caps

Thrombus scoring is to be performed at the end of dialyzer use for every dialyzer used in the study. Visual inspections of the dialyzer arterial and venous end caps will be done after the rinseback process has been completed by the clinical staff. This graded scoring method has been adopted from Dorsch et al.[2] and Laville et al.[3]

Grade 1	Grade 2	Grade 3	Grade 4
Good, clear dialyzer; no detectable clotting	Overall light redness; minimal clot formation	Overall moderate redness; clot formation but nonobstructive and dialysis still possible	Complete occlusion of the dialyzer rendering dialysis impossible
			

b) Bloodline Drip Chambers and Pods

Bloodline	Grade 1	Grade 2	Grade 3	Grade 4
Description	Clean dialysis blood line and bubble trap	Fibrin ring in the bubble trap or blood line	Nonobstructive clot in the blood line or bubble trap	Complete clotting and occlusion of the HD circuit rendering dialysis impossible
Examples of Chambers				
Examples of Pods				

This graded scoring method has been adopted from Islam et al.

Appendix III: New York Heart Association Functional Classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

References

[1]U.S. Department of Health and Human Services, Food and Drug Administration Guidance for Industry and Food and Drug Administration Staff. *Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies.* Document issued on: October 1, 2013

[2]Dorsch et al. *A multi-center, prospective, open-label, 8-week study of certoparin for anticoagulation during maintenance hemodialysis--the membrane study* BMC Nephrology 2012 Jun 28;13:50. doi: 10.1186/1471-2369-13-50.

[3]Laville et al. *Results of the HepZero study comparing heparin-grafted membrane and standard care show that heparin-grafted dialyzer is safe and easy to use for heparin-free dialysis.* Kidney Int. 2014 Dec ;86(6):1260-7. doi: 10.1038/ki.2014.225. Epub 2014 Jul 9.

[4]Islam MS, Hassan ZA, Chlamin F, Vido S, Berrada M, Verhelst D, Donnadiau P, Moranna O, Esnault V. Vitamin E-coated and heparin-coated dialyzer membranes for heparin-free hemodialysis: A multicenter, randomized, crossover trial. AJKD, 2016.