FRESENIUS MEDICAL CARE
RENAL THERAPIES GROUP (RTG), LLC

TITLE:	An Open-Label Clinical Study to Assess the Performance of the Dialyzer with Endexo™ in End-Stage Renal Disease Subjects
PROTOCOL NUMBER:	Endexo-001
INVESTIGATIONAL PRODUCTS:	Dialyzer with Endexo™, Fresenius Medical Care North America; Optiflux® dialyzer, Fresenius Medical Care North America (cleared under 510(k) number K152367)
SPONSOR:	Fresenius Medical Care RTG, LLC Medical Department, Clinical Research 920 Winter Street Waltham, MA 02451–1457
Amended:	Version 3.0 [dated 26/OCTOBER/2018]
	NCT03536663

1.0 PROTOCOL SYNOPSIS

Title	An Open-Label Clinical Study to Assess the Performance of the Dialyzer with Endexo™ in End-Stage Renal Disease Subjects
Protocol Number	Endexo-001
Study Type	Open-label single-arm clinical trial
Investigational Products	• Dialyzer with Endexo™ ("F5"), Fresenius Medical Care North America • Optiflux® dialyzer (F160NR), Fresenius Medical Care North America (cleared under 510(k) number K152367)
Proposed Indication	The dialyzers with Endexo are a series of single-use, high-flux dialyzers intended for treatment 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.
Study Objectives	The primary objective of the study is to collect data on the performance of the dialyzer with Endexo when used to perform hemodialysis (HD) in End-Stage Renal Disease (ESRD) subjects. The secondary objective is to collect and summarize adverse events with the dialyzer with Endexo when used to perform HD in ESRD subjects.
Study Design	This is a prospective, sequential, multi-center, open-label study with subjects on thrice-weekly (in-center) HD. After a Screening Period, there will be 12 HD treatments on the Optiflux dialyzer (Optiflux Period), followed by 38 HD treatments on the dialyzer with Endexo (Endexo Period), and then a Follow-up Visit.

Study Population	The study population will consist of ESRD subjects who are a minimum of 22 years of age, have been prescribed in-center thrice weekly HD continuously for at least 180 days prior to the date of signed informed consent, and have been prescribed the Optiflux F160NR dialyzer continuously for at least 30 days prior to the date of signed informed consent.
Total Number of Subjects	15-24 enrolled subjects, to achieve at least 12 subjects with a minimum of 36 HD treatments per subject on the dialyzer with Endexo
Total Number of Sites	3-4 (United States)
Estimated Duration of Study	Each subject will participate in the study for a maximum of 22 weeks. The Screening Period is up to 4 weeks. The Optiflux Period is 12 HD treatments on the Optiflux dialyzer (4 weeks in duration). The Endexo Period is 38 HD treatments on the dialyzer with Endexo (approximately 13 weeks in duration). There will be an in-center Follow-up Visit within 1 week of the subject's last HD treatment in the study. After the subject's last HD treatment in the study, the subject will resume HD with his/her physician-prescribed dialyzer.
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 continuously for at least 180 days prior to the date of signed informed consent 3. Has been prescribed the Optiflux F160NR dialyzer continuously for at least 30 days prior to the date of signed informed consent 4. Has a prescribed HD treatment time ≥180 minutes (3 hours)

	and ≤270 minutes (4.5 hours) at the time of signed informed consent 5. Has been on heparin anticoagulation for dialysis and has had no change in heparin prescription within 14 days prior to the date of signed informed consent 6. Has a most recent single pool Kt/V (spKt/V) ≥1.2 within 45 days prior to the date of a signed informed consent 7. Has a most recent hemoglobin ≥9 g/dL within 45 days prior to the date of a signed informed consent 8. Has a most recent platelet count ≥100,000/mm^3 within 45 days prior to the date of a signed informed consent 9. 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. Use of citric acid concentrate (such as Citrasate®) at the time of signed informed consent 2. Known allergic reactions to Endexo 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, or liver cirrhosis 5. Are receiving or have received chemotherapy / radiation therapy / plasmapheresis therapy within 90 days prior to the date of signed informed consent 6. Are receiving antibiotics or have used antibiotics within 14 days prior to the date of signed informed consent 7. Are currently enrolled in or have completed any other investigational product study within 30 days prior to the date of signed informed consent

	8. Has a life expectancy of less than 1 year
Study Endpoints	The primary endpoint is to collect data on the *in vivo* ultrafiltration coefficient (K_{uf}) of the dialyzer with Endexo during the first study use at 15 minutes (±5 minutes) after the recorded start of HD. The secondary endpoints include collecting the following data on the dialyzer with Endexo and the Optiflux dialyzer: • The number of any adverse events and device-related adverse events • Urea Reduction Ratio (URR) and spKt/V (calculated from pre- and post-HD BUN) for the first study use of the dialyzers • Pre- and post-HD albumin and beta-2-microglobulin for the first study use of the dialyzers
Additional Assessments	The following data will be collected on the dialyzer with Endexo and the Optiflux dialyzer: • Complement activation (C3a, C5a, SC5b-9) during the first study use of the dialyzer, collected pre-HD and at 30 minutes (±10 minutes) after the recorded start of HD • Thrombus scoring, performed at the end of dialyzer use for every dialyzer used in the study. The graded scoring method has been adopted from: 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. 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. • URR and spKt/V (calculated from pre- and post-HD BUN), every 3-4 weeks • Saline flushes and saline infusions during Optiflux and Endexo Periods o Total volume (mL) per treatment, time of

	administration and the reason The following data will be collected on the dialyzer with Endexo only: • Collect data on TMP and UFR for calculating the *in vivo* ultrafiltration coefficient (K_{uf}) of the dialyzer with Endexo at 15 minutes (±5 minutes) after the recorded start of HD during Visits 24, 27 and 30
Data Collection	The data listed below will be collected in the study. • Demographics • Medical History (and Historical Laboratory Values) • Concomitant Medications • Physical Exam, Vital Signs, Body Measurements (height, weight) • Adverse Events and Serious Adverse Events • Device Deficiencies • Laboratory Assessments • HD Prescription, HD Treatment Data, and HD Treatment-related Medications • Machine Readings of Ultrafiltration Rate and Transmembrane Pressure for K_{uf} estimation • Thrombus Scoring • Collection of time of administration and volume (mL) per saline flush and saline infusion during each study visit under Optiflux and Endexo periods
Sample Size Determination	The sample size of 15-24 subjects is based on FDA's Guidance for Industry and CDRH Reviewers: *Guidance for the Content of Premarket Notifications for Conventional and High Permeability Hemodialyzers (August 7, 1998)*, which recommends that data be collected for a minimum of 12 subjects receiving 36 treatments each.

Statistical Methods	Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented for continuous endpoints. Frequency and percent will be presented for categorical endpoints. Any missing values of an endpoint will be treated as completely missing at random and will not be imputed. Study analysis populations: • Safety population (spop): Subjects who sign the ICF, are eligible, are enrolled in the study, and have at least one HD treatment with the dialyzer with Endexo. • Analysis population (apop): Subjects who are in the spop, and have a minimum of 36 HD treatments with the dialyzer with Endexo. Analysis for primary endpoint: - For the K_{uf} for the dialyzer with Endexo, descriptive statistics will be presented. A 95% confidence interval will be calculated if appropriate. Analysis for secondary endpoints: - For URR and spKt/V for the first study use of both dialyzers, descriptive statistics will be presented, and a 95% confidence interval will be calculated if appropriate. - For albumin and beta-2-microglobulin, the relative percent change {((pre-HD – post-HD)/pre-HD) x 100} will be calculated. Descriptive statistics will be presented for the pre-HD and post-HD laboratory values and the relative percent change. The 95% confidence intervals will be calculated if appropriate. - Adverse events and device-related events per treatment will be calculated. The 95% confidence intervals will be derived if appropriate. Analysis for additional assessments: - For the measurements of complement activation, the relative percent change {((30 minutes after the recorded start of HD – pre-HD)/pre-HD) x 100} will be calculated. Descriptive statistics will be presented for the “pre-HD” and “30 minutes after the recorded start of HD” laboratory values and the relative percent change. The 95% confidence intervals will be calculated if appropriate. - For thrombus formation: • the number of subjects and percentages, and the number of HD treatments in each period for each grade category will be presented, and,

	• the proportion of treatments with full dialyzer clotting will be calculated for each subject in each period. Descriptive statistics of the proportions will be presented. A 95% confidence interval of the proportions will be calculated if appropriate. - As done for the analysis of the secondary endpoints, descriptive statistics will be presented for URR and spKt/V, and a 95% confidence interval will be calculated if appropriate.
Safety Monitoring	All adverse events and serious adverse events 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 course of 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.