CLINICAL TRIAL PROTOCOL

CLINICAL EVALUATION OF THE HEMOCARE™ HEMODIALYSIS SYSTEM FOR HOME NOCTURNAL HEMODIALYSIS

Protocol Number: DKPL-00057-001

[redacted]

NCT04087213

Sponsor: DEKA Research & Development

Sponsor Partner: CVS Kidney Care

Version Number: 1.6

21 January 2022

[redacted]

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LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CI	Confidence Interval
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESRD	End Stage Renal Disease
FDA	Food & Drug Administration
GCP	Good Clinical Practices
HD	Hemodialysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDEs	Investigational Device Exemptions
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention To Treat
NYHA	New York Heart Association
PD	Peritoneal Dialysis
PI	Principal Investigator
PP	Per Protocol
PRO	Patient Reported Outcomes
PT	Preferred Term
REB	Research Ethics Board
SAE	Serious Adverse Event
SOC	System Organ Class
UADE	Unanticipated Adverse Device Effect
UF	Ultrafiltration
URR	Urea Reduction Ratio

Investigator Protocol Signature Page

Study Title: Clinical Evaluation of the HemoCare™ Hemodialysis System for Home Nocturnal Hemodialysis

Protocol Number: DKPL-00057-001 v1.6

Final Date: 21 JANUARY 2022

Sponsor: DEKA R&D Corp

Sponsor Partner: CVS Kidney Care

Investigator Signature

I agree to abide by all the provisions set forth in the attached protocol. I also understand that these materials contain confidential information belonging to DEKA R&D Corp and CVS Kidney Care. Except as may be otherwise agreed to in writing, I agree to hold such information in confidence and not to disclose it to others (except where required by applicable law) nor use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, DEKA R&D Corp and CVS Kidney Care should be promptly notified.

I have access to the following Food and Drug Administration (FDA) regulations: 21 CFR Part 812, Investigational Device Exemptions; 21 CFR Part 50, Protection of Human Subjects; and 21 CFR Part 54, Financial Disclosure by Clinical Investigators.

I agree and/or certify that:

1. I will conduct the clinical investigation in accordance with this agreement, all requirements of the clinical investigational plan, IDE regulations, other applicable regulations of the FDA, and any conditions of approval imposed by my reviewing Institutional Review Board (IRB) /Independent Ethics Committee (IEC) or FDA and other Regulatory Authorities, e.g. Competent Authorities (when applicable). I agree to abide by all of the responsibilities of Investigators addressed under 21 CFR Part 812, Subpart E and Subpart G, including but not limited to the following:
    a. In the US, I will obtain written approval from the authorized IRB/IEC for the institution at which this investigation will be conducted. I will submit the certification of IRB/IEC approval and any conditions of this approval to the sponsor.
    b. I will ensure that Informed Consent is obtained from each subject participating in this clinical investigation in accordance with the informed consent regulation found in 21 CFR Part 50, and that a signed copy of the informed consent is available to the sponsor and their representatives, including the CRO.

c. I will supervise all testing of the device on human subjects and will allow only delegated physician sub-investigators to administer this devices and/or perform follow-up medical evaluations on the device.
d. I will be responsible for accountability of the device at the study site and, I will follow the instructions of the sponsor for reconciliation and return or disposal of the unused devices, as applicable.
e. I will ensure the accurate completion of clinical investigational plan/protocol case report forms and I will submit completed clinical investigational plan/protocol case report forms, progress reports, and a final report to the sponsor at the time frames specified in the clinical investigational plan/protocol and/or FDA regulations.
f. I will ensure timely reporting of Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs) in the Electronic Data Capture (EDC) as outline in the protocol.
g. I will direct the retention of required records and documents related to the investigation. Records shall be maintained during the investigation and for a period of two years following the date a marketing application is approved for the Investigational Product for the indication being investigated, or until three years after the Sponsor has provided written notice to the Investigator that the study or Investigational Product project has been discontinued.

2. I further certify that I have not been debarred under the Generic Drug Enforcement Act of 1992, 21 USC §§ 335a and 335b. In the event that I become debarred or receive notice of an action or threat of an action with respect to my debarment during the term of this Agreement, I agree to immediately notify the sponsor and the authorized IRB for my study site.

3. As required by 21 CFR Part 54, Financial Disclosure by Clinical Investigators, I will disclose sufficient and accurate financial information to the sponsor by completing and signing the Certification/Financial Disclosure Form. I will also notify the sponsor if my disclosed financial information changes at any time during the clinical investigation or up to one year following the closure of the study.

_____
Principal Investigator Name (printed)

_____ _____
Principal Investigator Signature Date

[redacted]

1 PROTOCOL SUMMARY

Protocol #:	DKPL-00057-001
Study Title:	Clinical Evaluation of the HemoCare™ Hemodialysis System for Home Nocturnal Hemodialysis
Product Name:	HemoCare™ Hemodialysis System
Indication:	The HemoCare™ Hemodialysis System is intended for hemodialysis treatment, including short daily and nocturnal hemodialysis, of renal failure patients. The HemoCare™ Hemodialysis System is intended for use in chronic dialysis facilities, self-care dialysis facilities, or the home setting. All treatments must be prescribed by a physician and administered by a trained operator. Treatments must be performed under the supervision or assistance of a medical professional or a care partner who has been trained and deemed competent in the use of the device by the prescribing physician.
Investigators:	Multi-center up to 10 sites in the United States
Study Objectives:	**Primary Objectives:** Safety To compare the safety of HemoCare™ Hemodialysis System, as measured by adverse events, between the Assisted and Unassisted Home Evaluable Periods. Performance To compare the performance of HemoCare™ Hemodialysis System, as measured by dialysis adequacy (weekly stdKt/V_{urea}), between the Assisted and Unassisted Home Evaluable Periods. **Secondary Objectives:** 1. To compare descriptively all reported adverse events (AE) and serious adverse events (SAE; anticipated, unanticipated, and device-related) between the Assisted and Unassisted Home Evaluable Periods. 2. To assess the safety of the treatment, as measured by control of serum phosphorus levels, during the Assisted and Unassisted Home Evaluable Periods. 3. To assess the safety of the treatment, as measured by control of serum potassium levels, during the Assisted and Unassisted Home Evaluable Periods.

	4. To evaluate UF data within and between the Assisted and Unassisted Home Evaluable Periods, as assessed by the difference between the fluid weight removed as measured by the device and the subject's weight change as measured by a scale.
Endpoints:	**Primary Endpoints:** **Primary Safety Endpoint:** Adverse event (AE) rate per 100 HemoCare™ Hemodialysis System treatments during Assisted and Unassisted Home Evaluable Periods **Primary Performance Endpoint** Weekly stdKt/Vurea as measured every two weeks during each Evaluable Period. **Secondary Endpoints:** 1. Number of anticipated and unanticipated AEs and SAEs during each Evaluable Period including number of device-related AEs and SAEs. 2. Incidences of decreased and increased post-dialysis serum phosphorus during each Evaluable Period. 3. Incidences of decreased and increased post-dialysis serum potassium during each Evaluable Period. 4. A descriptive summary of UF and target weight during each Evaluable Period. **Exploratory Endpoints:** 1. Reliability of HemoCare™ Hemodialysis System for the provision of treatments as scheduled and the ability to deliver prescribed treatments. 2. Proportion of subjects and care partners who successfully complete training with HemoCare™ Hemodialysis System and enter the Unassisted Home Evaluable Period. 3. Subjects' scores for Patient Recovery Time Questionnaire, Renal Treatment Satisfaction Questionnaire (RTSQ) and Care Partner scores for Zarit Burden Interview – 12 item version (ZBI-12).

	4. A descriptive summary by Evaluable Period of the total number of alarms, type of alarms and the time to resolve alarms will be provided.
Study Population:	Up to 70 subjects receiving HD may be enrolled in this study in order to achieve approximately 30 subjects entering the Unassisted Home Evaluable Period. No more than 25% of the total study subjects who complete the study may be enrolled at one site.
Study Duration:	Duration of Study participation will be documented by the Subject's active participation which is expected to be a minimum of 34 treatments per Evaluable Period.
Study Design and Methodology:	This is a prospective, multi-center, open-label, single-arm, cross-over study. A written informed consent will be obtained from each subject and care partner before starting any study related procedures. Subjects will undergo screening for eligibility during which inclusion and exclusion criteria will be evaluated. The screening period will be up to 30 days prior to enrollment. Eligible subjects will enter In-Facility Introduction Period during which they will begin training at the study site. This period will last approximately 1 to 6 weeks, but may be extended up to 12 weeks at the Investigator's discretion. The subjects will receive professionally attended Hemodialysis (HD) treatment with HemoCare™ Hemodialysis System at least 3 times every seven days. The duration of each HD treatment will be determined by the clinician on a case by case basis. Upon successful completion of training, the subjects will enter Transition Period A (1 to 2 weeks) which may occur at the study site or be transitioned to the home setting. The subjects will receive training and extended duration HD (5-10 hours per treatment) at least 3 times every seven days. This will be followed by the Assisted Evaluable Period during which the subjects will receive training and a minimum of 34 HD treatments (5-10 hours per treatment) with treatments prescribed to occur every other day, preferably in a home setting, with HemoCare™ Hemodialysis System. Alternatively, the treatment can also be administered at the study site based on clinician's judgment and/or subject's preference. The treatment will be administered by a Medical Professional during the Assisted Evaluable Period.

[redacted]

	After successful completion of the Assisted Evaluable Period, subjects will begin Transition Period B (1 to 2 weeks) and can be extended if additional training is required in the Home setting. The treatment during this Period could be performed in the absence of a Medical Professional, but they will visit the subjects' home if need be. This will be followed by the Unassisted Home Evaluable Period where subjects will receive a minimum of 34 HD treatments (5-10 hours per treatment) with treatments prescribed to occur every other day with HemoCare™ Hemodialysis System. Investigators will ensure the subjects' prescriptions achieve dialysis adequacy targets per local standard of care. The Investigator will evaluate any prescription changes during Evaluable Periods and they will be documented in the HemoCare™ Connectivity Platform. Trial subjects will be encouraged to remain in the same prescription frequency and duration in Assisted Evaluable Period and Unassisted Home Evaluable Period. Deviations in treatment frequency and duration can occur, on a treatment-by-treatment basis, within a range approved by the Investigator as stated in their care plan. AEs and dialysis system performance parameters will be collected throughout the study, but only AEs collected during the Evaluable Periods will be used for the comparison of safety between the two Evaluable Periods (Assisted and Unassisted).
Inclusion Criteria:	All of the following criteria must be met for the subject to be eligible for participation. The study will enroll subjects who: 1. Have been diagnosed with ESRD and are ≥ 18 years of age. 2. Are in stable clinical condition as judged by the treating physician, and confirmed by medical history, physical exam, and laboratory testing for 30 days prior to enrollment. 3. Have been receiving HD for at least 30 days prior to study enrollment, are expected to survive for at least 12 months and in the opinion of the Investigator are stable to start in the trial. 4. Have been dialyzing in a supervised medical facility or at home for ≥ 3 times per week. 5. Are willing to comply with the study requirements for training and therapy with HemoCare™ Hemodialysis System for the entire study treatment period.

[redacted]

	6. Understand English and can provide written informed consent (both the subject and care partner). 7. Are judged by the Investigator to be suitable for Home HD (the Investigator deems that with appropriate training, the subject and/or care partner will be able to successfully cannulate and/or manage the vascular access during the Unassisted Home Evaluable Period). 8. Have a stable functioning vascular access as judged by the treating physician. 9. Have a weekly stdKt/Vurea $\geq$ 2.0, an equivalent URR $\geq$ 0.65, or an equilibrated Kt/Vurea $\geq$ 1.0 on one occasion within 30 days prior to enrollment.
Exclusion Criteria:	If any of the following criteria are met, the potential subject will not be considered eligible for participation. The study will exclude subjects who: 1. Are pre-scheduled for a living donor transplant within the next 6 months. 2. Have a contraindication to heparin. 3. Are currently participating in another interventional study. 4. Have experienced an acute myocardial infarction with hospitalization, coronary artery bypass surgery, or acute coronary ischemia requiring angioplasty or stent insertion within 90 days of screening. 5. Have ongoing NYHA Class III or IV heart failure. 6. Have a significant psychiatric disorder or mental disability that could interfere with the subject's ability to provide informed consent and/or comply with study procedures. 7. Have ongoing sepsis or bacteremia and currently require IV antibiotics. 8. Have an allergy to polysulfone dialyzer. 9. Current self-reported pregnancy, actively planning to become pregnant within the next 12 months, lactating, or not using medically acceptable means of contraception during the study.

[redacted]

	10. Subject with fluid overload due to intractable ascites secondary to liver cirrhosis
Statistical Considerations:	**Determination of Sample Size:** With an underlying goal to have at least 1000 HemoCare™ Hemodialysis System treatments in both Evaluable Periods, at least 30 subjects will enter the Assisted Evaluable Period. No more than 25% of the total study subjects who complete the study may be enrolled at one site. Each patient is expected to contribute at least 68 evaluable treatments to the study (at least 34 in each Evaluable Period). Based upon the number of treatments and the expected rate of adverse events, the current study design is under-powered to detect a clinically meaningful (less than 10%) non-inferiority margin for the Unassisted Evaluable Period. For the primary performance endpoint, 'success' is defined as a subject who has all stdKt/Vurea measures in an evaluable period greater than or equal to 2.0. Several sets of simulation samples were generated (2,000 samples per set) assuming a rate of success between 95% and 99.5% and no actual difference between the two Evaluable Treatment Periods. The success rate of the 2 periods were compared and the CI interval for the differences were calculated. With 30 subjects in each Evaluable Period, a margin of 10% will provide 91% power to declare non-inferiority if the actual success rate is 99% and 83% power if the actual success rate is 98%. **Analysis Populations:** The Intent-to-Treat (ITT) population set will include all subjects who have used HemoCare™ Hemodialysis System at least once during the Assisted Evaluable Period. The Per Protocol (PP) population will include all subjects not having any enrollment violations and receiving at least 34 treatments in each Evaluable Period. The PP population will be used as sensitivity analyses of the primary safety endpoint and primary performance endpoint. Poolability of the data will be examined by assessing the heterogeneity of the primary endpoint results across sites with 5 or more subjects enrolled. **Primary Safety Endpoint:** The AE rate per 100 HemoCare™ Hemodialysis System treatments of Unassisted Home Evaluable Period will be compared to that of the

	Assisted Evaluable Period and a two-sided 90% CI will be generated for the rate ratio (λ_2/λ_1) comparing the relative difference in AEs for the two Evaluable Periods using a negative binomial regression model. **Primary Performance Endpoint:** Performance of the HemoCare™ Hemodialysis System will be assessed by weekly stdKt/V_{urea} that will be collected every two weeks during each Evaluable Period. During each Evaluable Period, a binary outcome variable will be defined to be 1 if the weekly stdKt/Vurea for a given week meets the success criteria and 0 otherwise. For each subject, this will result in approximately 5 binary outcome values for each period. Each subject will be considered as meeting the primary performance endpoint for that period if all weekly stdKt/Vurea values meet the performance success criterion. A Non-inferiority test will be conducted. The difference in proportion of subjects (P1-P2) meeting the performance criteria in the Unassisted Evaluation Period (P2) and the Assisted Evaluation Period (P1) will be reported with a two-sided 90% CI. If the Upper bound of the Confident interval is less than δ=0.10 then the null Hypothesis is rejected and non-inferiority is demonstrated. **Secondary Endpoints:** A descriptive summary of AEs including SAEs and other secondary endpoints will be provided. The details are provided later in the protocol. [redacted]

[redacted]

Table 1: Schedule of Evaluations and Procedures

Observation	Screening	In-Facility Introduction Period	Transition Period A	Assisted Evaluable Period[10,11]	Assisted Evaluable Period Visit 1	Transition Period B	Unassisted Home Evaluable Period	Unassisted Evaluable Period Visit 2	End of Study or Early Termination Visit
Informed Consent of subject and care partner	X								
Demographics and medical history	X								
Selected laboratory and medication histories (within 30 days of screening)	X								
Physical examination	X				X			X	X
Vital signs[1]	X				X			X	X
12-lead ECG	X								X
Feed water analysis for the home	X								
Home suitability assessment	X								
Clinical assessment by Investigator or designee[2]	X	X	X	X	X	X	X	X	
Clinical observations[3]		X	X	X		X	X		X
AE / SAE / ADE[4]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Ultrafiltration[5]		X	X	X		X	X		
Clinical laboratory examinations[6]	X	X	X	X		X	X		X
Patient reported outcomes[7]		X		X			X		X
HemoCare™ Hemodialysis System training		X	X	X					
Comprehension and retention testing[8]		X		X					
[redacted]									

1. Blood pressure, heart rate, respiratory rate, temperature (°F), height and weight are to be collected in a standardized manner in a sitting position after the patient has rested comfortably for 5 minutes.
2. A clinical assessment by the Investigator or designee will occur weekly throughout the study. A direct interaction with the subject is not required for this assessment.
3. Clinical observations will occur every treatment.
4. AEs and SAE's will be collected from the time of enrollment. ADEs will be collected from the first connection of HemoCare™ Hemodialysis System with the subject.
5. Ultrafiltration (UF) will be measured with every treatment throughout the study by HemoCare™ Hemodialysis System. Subject's weight will also be recorded before and after every treatment.
6. Clinical laboratory examinations are presented in Table 2.
7. Patient reported outcomes will include Renal Treatment Satisfactory Questionnaire (RTSQ), Patient Recovery Time Questionnaire and Zarit Burden Interview (ZBI-12) During In-Facility Introduction Period and Assisted Evaluable Period, patient reported outcomes will be collected during week 6. Patient reported outcomes will also be collected during week 6 of Unassisted Evaluable Period or at Early Termination,
8. Comprehension and retention assessment will occur at the end of the Assisted Evaluable Period.
[redacted]
10. Prior to the Assisted Evaluable Period, the Investigator must determine if the subject is clinically stable, including dry weight, and if the subject's medication prescriptions are stable, including dialysate composition, heparin, and anti-hypertensives.
11. Written confirmation for independent care is required at the end of the Assisted Evaluable Period.

[redacted]

Table 2: Schedule of Clinical Laboratory Examinations

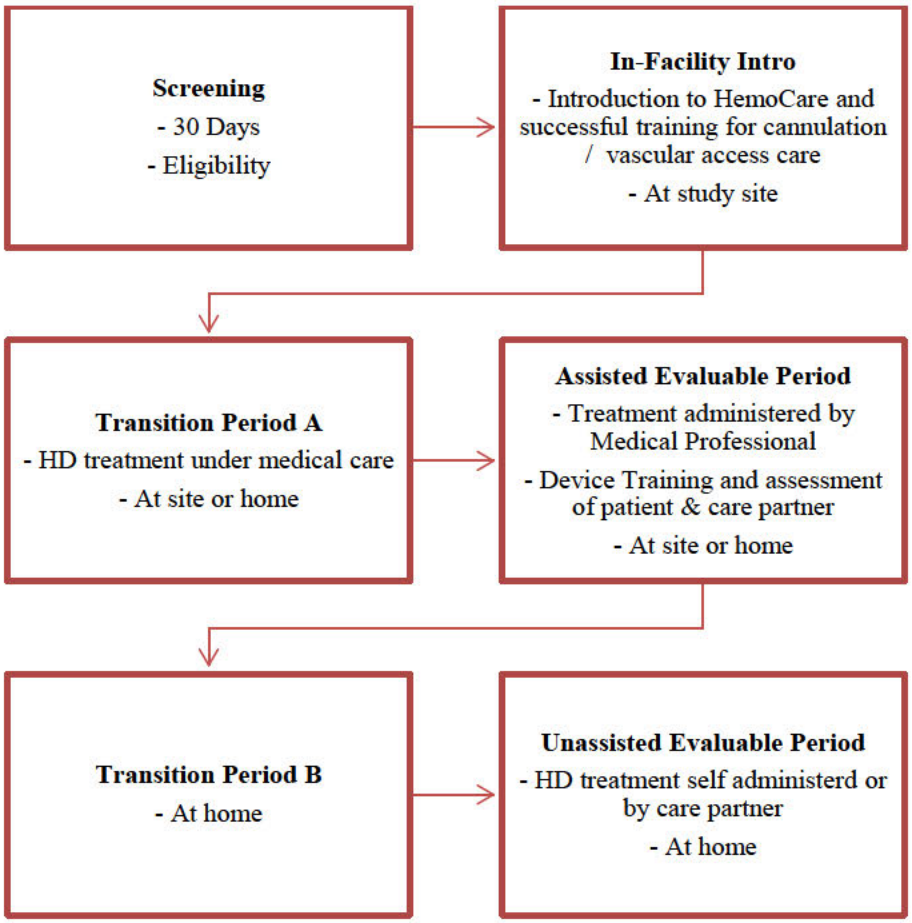
Observation	Screening	In-Facility Introduction Period	Transition Period A	Assisted Evaluable Period	Transition Period B	Unassisted Home Evaluable Period	End of Study or Early Termination Visit
CBC (pre-dialysis)[1]	X	X		X		X	X
Iron profile (pre-dialysis)[2]		X		X		X	X
Comprehensive metabolic panel (CMP) + serum phosphorus (pre-dialysis)[3]	X	X		X		X	X
Serum phosphorus and serum potassium (pre- and post-dialysis)[4]		X	X	X	X	X	
Urea (pre- and post-dialysis)[5]	X	X	X	X	X	X	
Kt/V calculation (pre- and post-urea)[5]	X	X		X		X	
aPTT[6]		X	X	X			

aPTT = activated partial thromboplastin time; CBC = complete blood count; CO_2 = carbon dioxide; ALP = alkaline phosphatase; ALT = alanine amino transferase; AST = aspartate amino transferase

1. A pre-dialysis CBC will be done at screening and monthly during the study.
2. A pre-dialysis iron profile (serum iron, TIBC, iron saturation and serum ferritin) will be done monthly during the study.
3. The comprehensive metabolic panel includes glucose, calcium, sodium, potassium, total CO_2 (or serum bicarbonate), chloride, urea, creatinine, ALP, ALT, AST, total bilirubin, serum albumin and total protein. In addition to serum phosphorus, the metabolic panel will be performed at screening and monthly during the study.
4. Pre- and post-dialysis serum potassium and serum phosphorus will be collected twice per week during Transition Period A and monthly for the remainder of the study
5. Kt/V is derived from pre-dialysis and post-dialysis serum urea levels. It will be performed once during Screening and the In-Facility Introduction Period, then every two weeks starting in the Assisted Evaluable Period. .
6. aPTT will be measured at the first treatment with HemoCare™ during the In-Facility Introduction Period, Transition Period A, and the Assisted Evaluable Period to assess anticoagulation [redacted] At the discretion of the Investigator, additional aPTT testing may be performed to assist with heparin dosing. [redacted]

[redacted]

Figure 1: Flow of activities:



[redacted]

2 INTRODUCTION

2.1 Study Rationale:

According to the 2017 United States (US) Renal Annual Data Report at the end of 2015, nearly 700,000 dialysis and transplant patients were receiving treatment for end-stage renal disease (ESRD). At the end of 2015, 85% of all prevalent cases receiving hemodialysis (HD) were receiving the same at an in-center setting. Overall survival probabilities for all dialysis patients remain poor. In the same US Renal Annual Data Report, the 5-year survival rate for HD patients was 42 %. Furthermore, on average, HD patients are hospitalized 1.7 times per year with an average length of stay being 11.4 days. In 2015, the overall costs to treat 434, 914 ESRD Medicare patients (<1% of all Medicare beneficiaries) were $33.9 Billion, accounting for 7 % of all Medicare spending.[1]

An expanding body of scientific literature indicates that clinical outcomes of suitable HD patients can be improved with HD treatments that are longer and/or more frequent in duration than conventional HD. A typical treatment schedule for the vast majority of HD patients in the US is 3 treatments per week, with each treatment lasting no more than 4 hours. In contrast, extended duration therapies can be 5 to 10 hours in duration and 3 to 6 times per week. Compared to conventional HD, these long dialysis therapies enable lower ultrafiltration (UF) rates and provide greater removal of middle molecules such as β2 microglobulin, higher phosphate clearances, and less fluctuation in electrolytes and extracellular fluids.[2] Compared to patients receiving conventional HD, patients treated with frequent nocturnal HD experience improved blood pressure control[3,4], improved serum phosphorus control[3,4], regression of left ventricular mass[3],and improved quality of life.[3]In an observational study of 177 patients treated with home frequent nocturnal HD, the 5 year survival rate was 85%, similar to the survival rate in a matched cadaveric renal transplant cohort.[5]

Short daily HD offers many of the same benefits as frequent nocturnal HD, but the latter is associated with greater uremic toxin clearances and perhaps greater improvements in cardiovascular health.[2-4] The risks associated with both short daily HD and frequent nocturnal HD are similar in many ways. More frequent use of the vascular access may be associated with greater risks of vascular access failure or infection. Increased blood and iron loss may occur with more frequent HD.

When performed in the home setting, the absence of immediate access to medical personnel and technical support places greater responsibility on patients and care partners for the management of the inherent risks associated with performing HD. Due to the timing (overnight) and duration of treatment, these risks may be greater with nocturnal HD, but can be mitigated with innovative safety features within HD devices, appropriate patient support and training, and provision of tools to allow remote monitoring of patient treatments by their healthcare professionals.

For logistical (patient and provider) and economic reasons, short daily HD or frequent nocturnal HD is typically performed in the home environment. Analysis of the US Renal Data System data from 2017 showed that despite the potential clinical and humanistic benefits, the delivery of HD

in the home environment in the US is limited to ~7000 patients, or just 1.4% of all dialysis patients.[1] Only a small minority of these patients perform home nocturnal HD.

The present study will evaluate safety and performance of a home-based HD system used for hemodialysis in nocturnal home settings.

[redacted]

3 Study Design

3.1 Overall Design

This is a prospective, multi-center, open-label, single-arm, cross-over study.

3.2 Rationale for Study Design

The HemoCare™ Hemodialysis System is designed to perform HD in a clinic setting, in a self-care setting, or in a home environment for conventional HD, short daily HD or extended-duration HD therapy during the daytime or at night dependent on the users' lifestyle or work schedule. The current study is designed specifically to gather and evaluate safety data for the use of the HemoCare™ Hemodialysis System (including labeling and training tools) during home nocturnal (during sleeping hours based on the patient schedule) use. Nocturnal HD therapy was chosen as a treatment in this study because of the clinical and humanistic benefits associated with it. In addition, its risk profile, especially when performed in a home setting, may be greater than either existing conventional or short daily HD therapies. In this regard, establishing an acceptable safety profile for home nocturnal HD therapy should be sufficient evidence to support conventional and short daily HD home therapies with HemoCare™ Hemodialysis System.

Subject and care partner training, comprehension and retention testing, are essential study elements. Written confirmation from the clinical staff affirming that the subject and care partner are capable of safely performing independent nocturnal HD treatments is also required and adds an additional threshold to ensure subject safety.

3.3 Duration of Treatment

Duration of Study participation will be documented by the Subjects' active participation which is expected to be a minimum of 34 treatments per Evaluable Period. It will include the following Periods:

Screening Period

Screening will be up to 30 days prior to Enrollment, during which time informed consent forms are signed and enrollment criteria are assessed.

In-Facility Introduction Period

The In-Facility Introduction Period is expected to last for approximately 1 to 6 weeks, but may be extended to 12 weeks if needed. During this time, subjects and their care partners, if the primary treatment administrator, will receive an introduction to the HemoCare™ Hemodialysis System, including basic device functions, general principles of dialysis, training on vascular access care and aseptic techniques. The trainer (a licensed Medical Professional – a dialysis nurse or other equivalent licensed Medical Professional, trained in the administration of hemodialysis and HemoCare™ Hemodialysis System) will work with the subject and their care partner to develop a care plan that establishes responsibilities for the subject and care partner for the remainder of the study, including the Unassisted Home Evaluable Period. This care plan will be used later to guide the use of the training materials in the Assisted and Unassisted Home Evaluable Periods. At a

minimum, the subject and care partner will be expected to successfully train on emergency procedures such as dialing 911, safely stopping treatment, disconnecting from HemoCare™ Hemodialysis System, and managing the vascular access during an emergency. At the end of the In-Facility Introduction Period, it is also expected that the subject or care partner can successfully cannulate the subject's fistula or AV graft, or access the dialysis catheter using aseptic technique.

The facility used for the In-Facility Introduction Period is intended to be a licensed medical facility where professional care may be provided and may include infusion centers, acute dialysis facilities, hospital rooms, and chronic dialysis facilities. Patients will be under the care of a licensed nephrologist and training and treatments will be provided by a licensed Medical Professional skilled in the administration of dialysis treatments and dialysis training.

During the In-Facility Introduction Period, the subjects will receive at least 3 professionally attended treatments every seven days. The duration of each treatment will be determined by the clinician to ensure the subject meets standard-of-care dialysis adequacy targets, and need not be constrained to extended duration HD treatments. Also during this period, the clinician will assess and adjust as necessary the heparin prescription to maintain desired levels of anticoagulation as guided by a heparin dosing protocol.

Transition Period A

After a successful In-Facility Introduction Period, the subject will continue to receive training while HD treatments are administered by a Medical Professional. The treatment setting may remain the same or it may transition to the home. The subject begins to receive at least 3 extended duration HD (5 to 10 hours per treatment) every seven days from a certified Medical Professional (dialysis nurse or other equivalent licensed medical professional, trained in the administration of hemodialysis and HemoCare™ Hemodialysis System). Treatments may occur at day or night as determined by the subject, care partner and Medical Professional. The duration of Transition Period A will be a minimum of 1 week and up to approximately 2 weeks. During this period, the Medical Professional will administer all treatments. In addition, the heparin prescription will be re-assessed and adjusted to maintain desired levels of anticoagulation according to the heparin protocol. Dialysate composition, oral phosphate binders, antihypertensive medications and other medications (e.g., EPO, vitamin D) may also be adjusted as needed. Written confirmation from the clinical staff affirming that the subject is sufficiently stable in prescription and dry weight is required to enter the Assisted Evaluable Period, otherwise additional weeks of Transition Period A may be allowed.

Assisted Evaluable Period

The Assisted Evaluable Period will be a minimum of 34 HD treatments (5-10 hours per treatment) with treatments prescribed to occur every other day. If the subject must go longer than one day between treatments, the reason will be documented in the source documents. The treatment will be administered preferably in a home setting. Alternatively, the treatment can also be administered at the study site based on clinician's judgment and/or subject's preference. Treatments will occur during subject's sleeping hours either at daytime or nighttime based on subject's daily schedule. During this period, the treatment will be administered by the Medical Professional. The Medical

Professional also uses the time to train the subject and care partner. Training will be hands-on and include the HemoCare™ Hemodialysis System training materials, the Patient HemoCare™ Hemodialysis System Checklist, and the Patient HemoCare™ Hemodialysis System Final Skills and Knowledge Check, as well as a refresher of training provided during the Introduction Period.

[redacted]

Investigators will ensure the subjects' prescriptions achieve dialysis adequacy targets per local standard of care. They will be instructed to document all changes made to the prescription during the Assisted Evaluable Period in the HemoCare™ Connectivity Platform. Deviations in treatment frequency and duration can occur, on a treatment-by-treatment basis, within a range approved by the Investigator as stated in their care plan. The subject and/or care partner will also be prompted to report any adverse events that may have been experienced during the Weekly Assessment (see Section 7.11), to ensure current and active capturing of the AEs. In addition, the subject and care partner will report data, medication use, pre- and post-dialysis weights, blood pressures, respiratory rate, body temperature, heart rate, and patient sleep durations via the HemoCare™ Hemodialysis System and the Treatment Flowsheet (see Section 7.11). Biochemical data (including complete blood count, iron profile, comprehensive metabolic panel, serum phosphorus, serum albumin, and serum urea) will be collected at least monthly during this period. Additionally, weekly stdKt/V_{urea} will be assessed every two weeks during this period. [redacted] Treatment data captured by the HemoCare™ Hemodialysis System includes all machine information, machine observations, and ultrafiltration information.

The Medical Professional will update the original care plan to clearly identify the responsibilities of the subject and his or her care partner throughout the Assisted Evaluable Period.

The Assisted Evaluable Period will conclude with a subject and care partner evaluation, including competency demonstration of all skills on HemoCare™ Hemodialysis System training skills checklist, depending on their defined responsibilities. Upon completion of the Assisted Evaluable Period, the Medical Professional must certify that the subject and/or care partner are sufficiently

[redacted]

trained to administer treatment without on-site professional assistance and that the subject is clinically stable (which includes a stable hemodialysis prescription and stable dry weight). If the subject or care partner is not sufficiently trained for unassisted home hemodialysis, additional training can occur during Transition Period B. No subjects will be allowed to perform dialysis in the absence of a Medical Professional, in either Transition Period B or the Unassisted Home Evaluable Period, without certification from the Medical Professional.

Transition Period B

During this 1 to 2 weeks transition period, the subject and care partner will perform each of their responsibilities under the care plan created with the Medical Professional. Duration of transition period may be extended if additional training is required. During this period, the Medical Professional will not be the primary individual administering treatment unless additional Subject training is required.

If the subject and care partner are certified for unassisted home hemodialysis using HemoCare™ Hemodialysis System, the Medical Professional will speak with the subject and/or care partner at least once per week during this period to address any concerns or challenges that the subject or care partner may be experiencing in the use of HemoCare™ Hemodialysis System. The Medical Professional may also visit the patient home, if need be. During this period the Subject and/or care partner will be prompted to report any adverse events that may have been experienced during the Weekly Assessment. This will allow active and current capture of any adverse events being experienced.

Unassisted Home Evaluable Period

The Unassisted Home Evaluable Period will be a minimum of 34 HD treatments (5-10 hours per treatment) with treatments prescribed to occur every other day, as prescribed by the Investigator. If the subject must go longer than one day between treatments, the reason will be documented in the source documents. Subjects will conduct the Unassisted Home Evaluable Period treatments during their sleeping hours either at daytime or nighttime based on subjects' schedules. The care partner must be present during all treatments during this period. Subjects will record how long they slept during dialysis in the Treatment Flowsheet.

Investigators will ensure the subjects' prescriptions achieve dialysis adequacy targets per local standard of care and that any prescription modifications will be done according to an established prescription change policy and will be recorded in the care plan. [redacted]

During this period subjects and/or care partners will be exclusively responsible for administering treatments. The Medical Professional will be available via telephone for support, but will not administer treatments during this period. The Medical Professional will speak with the subject and/or care partner at least once per week during this period to determine and document the

[redacted]

occurrence of any AEs. During the Weekly Assessment, the subject and/or care partner will be prompted to report any adverse events that may have been experienced to ensure current and active capturing of the AEs. In addition to the AE data, clinical data will be collected during this phase including medication use, pre- and post-dialysis weights, blood pressures, respiratory rate, body temperature, and heart rate. Biochemical data (including complete blood count, iron profile, comprehensive metabolic panel, serum phosphorus, serum albumin, and serum urea) will be collected at least monthly during this period. Additionally, weekly stdKt/V_{urea} will be assessed every two weeks during this period. [redacted]

The Unassisted Home Evaluable Period will conclude after a minimum of 34 treatments (5-10 hours in length). If the subject successfully completes the study, seamless enrollment into the Extension Study (DKPL-00674-001: An Open Label Study to Allow Patients Continuous Use of the HemoCare™ Hemodialysis System for Home Hemodialysis Prior to Market Authorization) is possible, for continued access to the device. If the subject elects not to enroll in the Extension Study, or does not successfully complete the study, the subject will resume HD therapy on another device as prescribed by their regular physician.

4 Objectives and Endpoints

4.1 Objectives

4.1.1 Primary Objectives

Safety
To compare the safety of HemoCare™ Hemodialysis System, as measured by adverse events, between the Assisted and Unassisted Home Evaluable Periods.

Performance
To compare the performance of HemoCare™ Hemodialysis System, as measured by dialysis adequacy (weekly stdKt/V_{urea}), between the Assisted and Unassisted Home Evaluable Periods

4.1.2 Secondary Objectives:

1. To compare descriptively all reported adverse events (AE) and serious adverse events (SAE; anticipated, unanticipated, and device-related) between the Assisted and Unassisted Home Evaluable Periods.

2. To assess the safety of the treatment, as measured by control of serum phosphorus levels, during the Assisted and Unassisted Home Evaluable Periods.

[redacted]

3. To assess the safety of the treatment, as measured by control of serum potassium levels, during the Assisted and Unassisted Home Evaluable Periods.

4. To evaluate UF data within and between the Assisted and Unassisted Home Evaluable Periods, as assessed by the difference between the fluid weight removed as measured by the device and the subject's weight change as measured by a scale.

4.2 Endpoints

4.2.1 Primary Endpoints

4.2.1.1 Primary Safety Endpoint

Adverse event (AE) rate per 100 HemoCare™ Hemodialysis System treatments during Assisted and Unassisted Home Evaluation Periods

4.2.1.2 Primary Performance Endpoint

Weekly stdKt/Vurea as measured every two weeks during each Evaluable Period

4.2.2 Secondary Endpoints

1. Number of anticipated and unanticipated AEs and SAEs during each Evaluable Period including number of device-related AEs and SAEs.

2. Incidences of decreased and increased post-dialysis serum phosphorus during each Evaluable Period.

3. Incidences of decreased and increased post-dialysis serum potassium during each Evaluable Period.

4. A descriptive summary of UF and target weight during each Evaluable Period.

[redacted]

[redacted]

5 Study Population

5.1 Inclusion Criteria

All of the following criteria must be met for the subject to be eligible for participation. The study will enroll subjects who:

1. Have been diagnosed with ESRD and are ≥ 18 years of age.

2. Are in stable clinical condition as judged by the treating physician, and confirmed by medical history, physical exam, and laboratory testing for 30 days prior to enrollment.

3. Have been receiving HD for at least 30 days prior to study enrollment, are expected to survive for at least 12 months and in the opinion of the Investigator are stable to start in the trial.

4. Have been dialyzing in a supervised medical facility or at home for ≥ 3 times per week.

5. Are willing to comply with the study requirements for training and therapy with HemoCare™ Hemodialysis System for the entire study treatment period.

6. Understand English and can provide written informed consent (both the subject and care partner).

7. Are judged by the Investigator to be suitable for Home HD (the Investigator deems that with appropriate training, the subject and/or care partner will be able to successfully cannulate and/or manage the vascular access during the Unassisted Home Evaluable Period).

8. Have a stable functioning vascular access as judged by the treating physician.

9. Have a weekly stdKt/Vurea ≥ 2.0, an equivalent URR ≥ 0.65, or an equilibrated Kt/Vurea ≥ 1.0 on one occasion within 30 days prior to enrollment.

5.2 Exclusion Criteria

If any of the following criteria are met, the potential subject will not be considered eligible for participation. The study will exclude subjects who:

[redacted]

1. Are pre-scheduled for a living donor transplant within the next 6 months.
2. Have a contra-indication to heparin.
3. Are currently participating in another interventional study.
4. Have experienced an acute myocardial infarction with hospitalization, coronary artery bypass surgery, or acute coronary ischemia requiring angioplasty or stent insertion within 90 days of screening.
5. Have ongoing NYHA Class III or IV heart failure.
6. Have a significant psychiatric disorder or mental disability that could interfere with the subject's ability to provide informed consent and/or comply with study procedures.
7. Have ongoing sepsis or bacteremia and currently require IV antibiotics.
8. Have an allergy to polysulfone dialyzers.
9. Current self-reported pregnancy, actively planning to become pregnant in the next 12 months, lactating, or not using medically acceptable means of contraception during the study.
10. Subject with fluid overload due to intractable ascites secondary to liver cirrhosis

5.3 Subject Discontinuation/Withdrawal

Subjects may be withdrawn/prematurely discontinued from the study if their participation is discontinued before completion of the Unassisted Evaluation Period. The reason(s) could include:

1. Adverse event(s) (AEs)
2. Inadequate dialysis
3. Protocol violations (i.e., the subject failed to meet protocol entry criteria or did not adhere to the protocol requirements)
4. Pregnancy, lactating or not using medically acceptable means of contraception (confirmed by Investigator)
5. Lost to follow-up (i.e., subject fails to return for study visits)
6. Voluntary withdrawal (i.e., subject's request)

7. Termination of the study
8. Investigator's discretion
9. Renal transplantation
10. Switch to Peritoneal Dialysis (PD)
11. Subject death
12. Other reason (with reason noted on the electronic case report form [eCRF])

The Investigator may terminate a subject's study participation at any time during the study if he/she judges it to be in the subject's best interest. In addition, a subject may discontinue his or her participation at any time during the study. If a subject's participation is discontinued, the reason(s) must be recorded in the source documents and on the eCRFs. If a subject discontinues for any reason, every effort should be made to perform all of the procedures that are scheduled for the last visit. In addition, adverse device effects (ADEs) and all serious adverse events (SAEs), related to study treatment or not, will be followed post-study by the Investigator until the subject is stable or the situation is resolved.

Discontinued subjects will not be replaced unless the targets for enrollment/treatments will not be achieved with the current active group of study subjects. The Investigator or designee should inform their site monitor the moment any subject is discontinued from the study.

5.4 Screen Failures

Subjects not found eligible to be entered into In-Facility Introduction Period post consenting will be deemed as screen failures. These subjects will not be included in the 70 subjects enrolled in this study.

6 Study Intervention

6.1 Description of the Study Device

The HemoCare™ Hemodialysis System is comprised of the following components:

- HemoCare™ Treatment Device
- HemoCare™ Blood Treatment Set (BTS)
- HemoCare™ Bicarbonate Concentrate Set
- HemoCare™ Water Device
- HemoCare™ Connectivity Platform

[redacted]

[redacted]

[redacted]

6.1.3 Accessibility and Control of Study Participant Data

In order to ship investigational product, service investigational devices to/at subjects' homes, [redacted] a subset of sponsor personnel and designees will need access to shipping addresses/contact information. A study-specific procedure will be created and implemented by DEKA R&D and CVS Kidney Care to document how they will collect, control, and secure subjects' contact information and addresses. Access to the collected data will be restricted to the teams/team members who need the information to appropriately conduct this study. Study subjects will have the ability to notify study personnel of service needs to ensure timely installation/service of device and supply delivery.

Sponsor or designees will service devices directly in subjects' homes, collect blood and [redacted]/water samples, and designated couriers will deliver specified investigational and non-investigational product (e.g., acid concentrate and HemoCare™ Bicarbonate Concentrate Set) directly into subjects' homes. These groups will communicate through the study sites to minimize direct patient interaction where appropriate. The Sponsor will ultimately redact all collected confidential information from study documentation when subjects end their study participation and all investigational products are removed from the subjects' homes [redacted]

6.1.4 Study Treatments Administered

All subjects who sign the informed consent form (ICF) (see Section 11.4) will be assigned a subject number.

[redacted]

All enrolled subjects will receive HemoCare™ Hemodialysis System treatments. The frequency and duration of treatment will vary according to the study period, the subject's prescription from his/her treating physician and in accordance to the local standards of care. The duration and frequency of HD treatment during the In-Facility Introduction Period will be determined by physician. Thereafter the subject will receive extended duration HD treatment (5-10 hours per treatment). During the Evaluable Periods of the study, dialysis treatment will be given at least every other day when feasible. Whereas, during the transition Periods A and B, the extended HD treatment will be given at least 3 times every 7 days.

An existing functioning vascular access (AV fistula or graft, or dual lumen tunneled catheter) will be used for dialysis. Treatments will be administered by trained clinic staff and/or trained subject and care partner.

Within each Evaluable Period, blood flow rate will remain consistent, and trial subjects will be encouraged to keep the HD treatment duration and frequency similar in both Periods. Deviations in treatment frequency and duration can occur, on a treatment by treatment basis, but must be within a range approved by the Investigator. [redacted]

The delivered doses of dialysis will be monitored for each subject using the weekly stdKt/Vurea every two weeks during each Evaluable Period. The delivered dialysis dose in terms of stdKt/Vurea will be determined by collecting pre- and post-dialysis blood (urea) samples and utilizing computational methods based on urea kinetic modeling.

6.2 Prohibitions and Restrictions

There are no activity or diet restrictions specific to the study. Subjects should discuss their daily diet and activities with their physician.

6.3 Prior and Concomitant Therapy

The Investigator should review any additions or changes in concomitant therapy. All medications should be recorded in the source documents or equivalent. Prior medications defined as those taken during the 30 days prior to enrollment, will be recorded on the eCRF. Concomitant medications, including dose, frequency, start, stop dates, and indication for use, will be recorded on the eCRF throughout the study. Heparin prescription and any dose changes administered during dialysis will be recorded.

6.4 Excluded Concomitant Medications

Use of IV antibiotics during the study will be restricted during dialysis treatment. IV antibiotics should be administered before or after the treatment as prescribed by physician. No other

intravenous medications (other than heparin [redacted] may be administered once the patient connects to the device or during treatment.

7 Study Schedule and Procedures

7.1 Schedule of Evaluations and Procedures

All clinical study evaluations will be performed according to Table 1, Schedule of Evaluations and Procedures, and the instructions listed below. If a subject 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).

7.1.1 Screening Period

Screening will be conducted within 30 days of enrollment. The study must be explained to the subjects and care partners at this visit, and all subjects must sign an ICF before any study-related procedures are performed. The following procedures will be performed and, as appropriate, recorded on the eCRF at the Screening visit.

- Informed consent of the subject
- Demographics and medical history
  - Dialysis prescription, including their start weight, end weight, and total fluid weight removed for the 6 dialysis sessions prior to enrollment
  - Type of vascular access
  - Discuss travel or relocation plans
  - Subject reported history of AEs during HD treatment
- Laboratory and medication histories (within 30 days of Screening)
- Anticoagulation regimen [redacted]
- Physical exam including weight and height
- Vital signs
- 12-lead ECG
- Feed water analysis for the home
- Home suitability assessment
- Inclusion and Exclusion criteria assessment by the Investigator or designee
- Adverse events/serious adverse events/adverse device effects during the screening period
- Concomitant medications
- Clinical laboratory evaluations
- Enrollment in the study for all eligible subjects

For screen failed subjects, the consent date of the subject and inclusion/exclusion criteria will be collected.

7.1.2 In-Facility Introduction Period

This period is expected to last for 1 to 6 weeks, but may be extended to 12 weeks if needed. The following procedures or evaluations will be performed:

[redacted]

- Treatment with HemoCare™ Hemodialysis System at least 3 times every seven days; duration of each treatment will be selected by the Investigator to ensure the subject is meeting their targets for dialysis adequacy. All treatment-related data will be captured by HemoCare™ Hemodialysis System and sent to the study's electronic database.
- Treatment parameters (including heparin prescription) will be assessed and adjusted to maintain desired levels.
- In addition to standard hematology and chemistries, samples for aPTT will be measured as specified in Table 2 to assess anticoagulation and obtain optimal heparin dosing as applicable for the subject. At the discretion of the Investigator, additional aPTT testing may be ordered.
- Training of subject and care partner by site staff during initial 6 HD treatments on the assessment of blood treatment set.
- Patient Reported Outcomes (collected during the In-Facility Introduction Period).
- Additionally, at each treatment, the following data will be collected:
    - Clinical observations
    - Adverse events/serious adverse events/adverse device effects
    - Concomitant medications
    - Treatment data from HemoCare™ Treatment Device
    - Visual assessment of the HemoCare™ Blood Treatment Set
    - Device-related product issues (Device-related product complaints)
    - Chloramine, and if applicable, pH and conductivity testing
- [redacted]
- The Investigator or designee will assess each subject on a weekly basis according to standard of care during the Treatment Period. The assessment may include blood pressure, fluid status and dialysis prescription.
- Installation of HemoCare™ Hemodialysis System into the subject's home may occur during this period.
- In-Facility Introduction period concludes with:
    - The Investigator must reassess the stability of the subject during the In-Facility Introduction Period. Once the clinician concludes that the subject is clinically stable and their HD prescription, including dry weight, is stable, then the subject can transition into Transition Period A.

7.1.3 Transition Period A

This period will be minimum 1 week and up to approximately 2 weeks. The following procedures or evaluations will be performed:

- Treatment with HemoCare™ Hemodialysis System at least 3 times every seven days, 5-10 hours per treatment at study site or in a home setting during day time or night time based on subject's schedule. The subject will receive each treatment from a certified Medical professional (dialysis nurse or other equivalent medical professional). Treatment-related data will be captured by HemoCare™ Hemodialysis System.

[redacted]

- Heparin prescription, oral phosphate binders and anti-hypertensive medications will be assessed and adjusted as needed.
- Clinical laboratory evaluations as specified in Table 2. At the discretion of the Investigator, additional aPTT testing may be ordered for study treatments during this period.
- Training of subject and care partner by site staff during initial 6 HD treatments on the assessment of blood treatment set.
- Additionally, at each treatment, the following data will be collected:
  - Clinical observations
  - Adverse events/serious adverse events/adverse device effects
  - Concomitant medications
  - Treatment data from HemoCare™ Treatment Device
  - Visual assessment of the HemoCare™ Blood Treatment Set
  - Device-related product issues (device-related product complaints)
  - Chloramine, and if applicable, pH and conductivity testing
- The Investigator or designee will assess each subject on a weekly basis according to the care plan during the Treatment Period. The assessment may include blood pressure, fluid status and dialysis prescription.

7.1.4 Assisted Evaluable Period

This period will last a minimum of 34 treatments during which time the Medical Professional will perform each treatment. The following procedures or evaluations will be performed:

- Treatment with HemoCare™ Hemodialysis System in preferably a home setting (may be shifted to site based on Investigator's judgment and/or subject's preference) will be a minimum of 34 HD (5-10 hours per treatment) with treatments prescribed to occur every other day. Treatment-related data will be captured by HemoCare's™ Connectivity Platform.
- Treatments will occur during subject sleeping hours either at daytime or nighttime based on subject's daily schedule. Subsequent to each treatment, all patients will be asked to document if they slept during dialysis, and if so, for what length of time.
- Clinical laboratory evaluations as specified in Table 2. At the discretion of the Investigator, additional aPTT testing may be ordered for study treatments during this period.
- Training of subject and care partner by site staff during initial 6 HD treatments on the assessment of blood treatment set.
- Patient Reported Outcomes
- Additionally, at each treatment, the following data will be collected:
  - Clinical observations
  - Adverse events/serious adverse events/adverse device effects – collected by a Medical Professional administering treatment, the subject, or care partner
  - Concomitant medications
  - Treatment data from HemoCare™ Treatment Device

- Visual assessment of the HemoCare™ Blood Treatment Set
- Device-related product issues (Device-related product complaints)
- Chloramine, and if applicable, pH and conductivity testing
- [redacted]
- Period concludes with successful comprehension and retention assessment for the subject and care partner.
- The Investigator or designee will assess each subject on a weekly basis according to care plan during the period. The assessment may include blood pressure, fluid status and dialysis prescription.
- Subject and/or care partner will be trained on the assessment of the HemoCare™ Treatment Set to determine if it should be replaced before the next treatment.
- Subject and/or care partner will receive HemoCare™ Hemodialysis System specific device training for self-dialysis.
- Written confirmation from the clinical staff affirming that the subject and care partner) are capable and safe to perform independent nocturnal HD treatments.
  - *Note: Subjects may exit the Assisted Evaluable Period before training is complete if all required treatments have been performed. Treatment of these subjects will continue to be administered by a medical professional in Transition B Period until such time that clinical staff is able to affirm subject and care partner training and capability to safely perform independent nocturnal HD treatments.*
- Installation of HemoCare™ Hemodialysis System into the subject's home will be targeted during this period if it has not occurred earlier.

7.1.5 Assisted Evaluable Period Visit 1

On-site visit will be conducted at Week 3 of the Assisted Evaluable period. The following assessments will be performed:

- Physical Exam
- Vital signs
- Adverse Events/Serious Adverse Events assessment and confirmation
- Concomitant medications
- Care Plan review and prescription adjustment, if needed.

Additional procedures might be performed based on the Investigator's judgment.

7.1.6 Transition Period B

This period will be 1-2 weeks in duration, but may be longer if the subject and/or care partner requires more training. During this period the subject and/or care partner performs each extended duration treatment with HemoCare™ Hemodialysis System in the subject's home. If the subject and/or care partner are not certified to perform HD treatment, a Medical Professional must perform the treatment. The following information will be collected and procedures or evaluations will be performed:

[redacted]

- Treatment with HemoCare™ Hemodialysis System prescribed to occur every other day (5-10 hours per treatment). On a case-by-case basis, clinical staff may accompany the subject as necessary for the Transition Period B HD treatments in the home, if deemed appropriate by the dialysis clinic. Treatment-related data will be captured by HemoCare™ Connectivity Platform.
- Clinical laboratory evaluations as specified in Table 2. At the discretion of the Investigator, additional aPTT testing may be ordered for study treatments during this period.
- Care partner will be present for all treatments for which a Medical Professional is not present during this period.
- Additionally, at each treatment, the following data will be collected:
  - Clinical observations
  - Adverse events/serious adverse events/adverse device effects – collected by a Medical Professional during the weekly call
  - Concomitant medications
  - Treatment data from HemoCare™ Treatment Device
  - Visual assessment of the HemoCare™ Blood Treatment Set
  - Device-related product issues (Device-related product complaints)
  - Chloramine, and if applicable, pH and conductivity testing
- The Investigator or designee will assess each subject on a weekly basis according to care plan during this Period. The assessment may include blood pressure, fluid status and dialysis prescription.

7.1.7 Unassisted Home Evaluable Period

This period will last a minimum of 34 treatments during which time the subject and/or care partner will perform each treatment in the subject's home. The following information will be collected and procedures or evaluations will be performed:

- A minimum of 34 nocturnal HD treatments with HemoCare™ Hemodialysis System (5-10 hours per treatment) with treatments prescribed to occur every other day. Treatment-related data will be captured by HemoCare™ Connectivity Platform.
- Clinical laboratory evaluations as specified in Table 2. At the discretion of the Investigator, additional aPTT testing may be ordered for study treatments during this period.
- Care partner will be present for all treatments during this period.
- Patient Reported Outcomes
- Additionally, at each treatment, the following data will be collected:
  - Clinical observations
  - Adverse events/serious adverse events/adverse device effects – collected by a Medical Professional during the weekly call
  - Concomitant medications
  - Treatment data from HemoCare™ Treatment Device
  - Visual assessment of the HemoCare™ Blood Treatment Set

- Device-related product issues (Device-related product complaints)
- Chloramine, and if applicable, pH and conductivity testing
- [redacted]
- The Investigator or designee will assess each subject on a weekly basis according to care plan during the Treatment Period. The assessment may include blood pressure, fluid status and dialysis prescription

7.1.8 Unassisted Home Evaluable Period Visit 2

Visit 2 will be conducted at Week 3 of the Unassisted Evaluable period. The following assessments will be performed:

- Physical Exam
- Vital signs
- Adverse Events/Serious Adverse Events assessment and confirmation
- Concomitant medications
- Care Plan review and prescription adjustment, if needed.

Additional procedures might be performed based on the Investigator's judgment.

7.1.9 End of Study Visit or Early Termination Procedures

The following information will be collected and procedures or evaluations will be performed at the final visit (in-facility after completion of the Unassisted Home Evaluable Period):

- Patient Reported Outcomes (collected during Week 6 of Unassisted Home Evaluable Period or following Early Termination)
- Physical exam including weight
- Vital signs
- 12-lead ECG
- Adverse events/serious adverse event/adverse device effect
- Concomitant medications
- Clinical laboratory evaluations as specified in Table 2
- Device-related product issues (device-related product complaints)
- Device related AEs and SAEs will be followed post-study until resolution

If a subject discontinues from the study prematurely, every attempt should be made to perform all of the procedures and evaluations that are scheduled for the final visit (i.e., End of Study Visit). Upon exiting the study, subjects who discontinued early will be transitioned to a conventional HD device. HemoCare™ Hemodialysis System used for these subjects will be removed from their home.

For subjects who successfully complete the study, the site should schedule the End of Study Visit to coincide with the Qualification Visit of the Extension Study (DKPL-00674-001: An Open Label Study to Allow Patients Continuous Use of the HemoCare™ Hemodialysis

[redacted]

System for Home Hemodialysis Prior to Market Authorization), to allow for seamless enrollment and continued access to the HemoCare™ Hemodialysis System in the home.

7.2 Study Activities

7.2.1 Enrollment

A subject will be considered enrolled in the study on the date the Investigator or designee confirms all inclusion criteria are met, no exclusion criteria are present, the subject's residence is capable of hosting the HemoCare™ Hemodialysis System, and informed consent has been obtained. This confirmation may be documented in writing (via the Enrollment Approval template) or electronically (via a medical record entry or by email with signature and date/time stamp).

7.2.2 Demographics and Baseline Characteristics

A complete medical history will include a review of all major body systems and medical history, as applicable. Information regarding the type and frequency of dialysis therapy received prior to enrollment in this study and type of access will be obtained.

Demographics will include the age, gender, race, and ethnicity.

7.2.3 Physical Examination

Physical examinations will be performed during Screening, Assisted Evaluable Period Visit 1, Unassisted Evaluable Period Visit 2, and at End of Study visits.

Any new condition or worsening of a pre-existing condition from Screening will be noted and recorded on the AE eCRF page. Height will be measured at Screening only.

Weight will be measured at Screening and at the End of Study visit. Additional collection of pre- and post-treatment weights will occur as noted in Section 7.10.

An attempt should be made to perform a final physical examination on subjects who complete Screening and enter the study, but who discontinue from the study early, particularly if the subject is discontinuing from the study because of an AE.

7.2.4 Vital Signs

Vital signs will include measurements of height, weight, sitting blood pressure, sitting respiratory rate, temperature, and sitting pulse rate. Vital signs will be obtained at Screening, Assisted Evaluable Period Visit 1, Unassisted Evaluable Period Visit 2, and at the End of Study visit. Additional vital signs will be collected during treatment times and are explained in Section 7.10, Clinical Observations.

7.2.5 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed during Screening and the End of Study visit. The 12-lead ECG will be performed after the subject has been resting in a supine position for 5 minutes. Any abnormal findings will be recorded and abnormal changes from the Screening ECG will be considered AEs.

7.2.6 Kt/V

Weekly stdKt/Vurea will be calculated from pre- and post-dialysis urea levels during each evaluable period. Blood samples will be obtained every two weeks during each Evaluable Period. A central laboratory will be used for the analysis of the blood samples. If the weekly stdKt/Vurea goal is not met, the reason will be recorded.

Study personnel will be trained to obtain the pre- and post–treatment blood samples based on the Kidney Disease Outcome Quality Initiative Guidelines for sample collection.

7.3 Reliability of HemoCare™ Hemodialysis System

Treatments will be classified as either complete (receiving at least 90% of planned treatment time), incomplete (receiving less than this), or missed altogether. Planned treatment will be defined as the treatment time selected and confirmed by the user at the start of each treatment. For all incomplete and missed treatments, the Medical Professional will record a reason in the eCRF.

7.4 Training on HemoCare™ Hemodialysis System and Study Procedures

7.4.1 Study Site Team Training

The assigned site team members (investigators and nurses) will be trained on HemoCare™ Hemodialysis System by the Sponsors (or designee) as part of site initiation. HemoCare™ Hemodialysis System training tools developed specifically for use with HemoCare™ Hemodialysis System will be utilized. Assigned site team members will be required to complete and pass a skill assessment before they are approved to train enrolled subjects at their site. The skill assessment includes the Nurse Skills Checklist and the Nurse Final Knowledge Check.

All assigned site team members will also receive study training specific to their study role (e.g., protocol, eCRF, laboratory procedures) prior to starting study activities.

7.4.2 Subject and Care Partner Training

Enrolled subjects and care partners will receive training during the In-Facility Introduction Period as specified above. Approved site training nurses will conduct all subject and care partner training utilizing HemoCare™ Hemodialysis System training tools. Enrolled subjects and care partners will be required to demonstrate competency of a skills assessment commensurate with their responsibilities as defined in the care plan in order to complete the In-Facility Introduction Period.

[redacted]

7.6 Patient Reported Outcomes

Clinical outcomes will be documented as part of objective clinical assessment. Patient reported data will be collected as shown in Table 4.

Table 4. Patient Reported Outcomes

Patient Reported Outcomes (PRO)	Collection Time Point						
	Screening Period	In-Facility Introduction Period	Transition Period A	Assisted Evaluable Period	Transition Period B	Unassisted Evaluable Period	End of Study Visit
Renal Treatment Satisfactory Questionnaire (RTSQ)		X		X		X	X
Patient Recovery Time Questionnaire		X		X		X	X
Zarit Burden Interview (ZBI-12)		X		X		X	X

Trial subjects and/or care partners will complete patient reported outcomes (PROs) independently and the completed questionnaires will be transferred into the Electronic Data Capture (EDC) system. Study sites will be instructed to review the completed questionnaires and follow up with the study subjects if necessary based on their responses.

7.7 Ultrafiltration

HemoCare™ Hemodialysis System calculates fluid removal based on the subject's starting weight, target weight, prime and rinse back volume, and any additional fluid adjustments made by the user. Ultrafiltration (UF) removed is the total volume of fluid removed during a dialysis treatment. Fluid weight removed is total UF removed minus prime and rinseback volumes and any fluid adjustments. Target weight is the goal weight prescribed for a given treatment. Starting weight is the weight of the subject pre-treatment. The UF goal is the difference between the starting weight and target weight, with the addition of prime and rinseback volumes, and any fluid adjustments (such as oral intake during treatment).

[redacted] In addition, the subject's weight will also be measured before and after each treatment and recorded in the device. Calibrated digital scales will be provided. Subjects will measure their pre- and post-dialysis weight. Subjects will record the volume or weight of any fluid they plan to

consume during treatment. [redacted] Subjects will be encouraged to restrict output to before pre-treatment weight or after post-treatment weight (where possible).

To minimize variability in this measurement, clinic staff and subjects will be instructed to use a digital scale and the same scale for all study treatments and to standardize clothes and shoes worn by the subject at the pre-dialysis and post-dialysis weighing. All training, supplies, and techniques utilized by the subject during the Assisted Evaluable Period must be similarly utilized during the Unassisted Home Evaluable Period.

[redacted]

This UF goal can be adjusted during the dialysis session [redacted]

During both Evaluable Periods, the user will be limited in the UF adjustments they can make at the start of and during treatment. Prior to treatment and during treatment, the user can adjust UF goal and treatment time within ranges pre-set by the Investigator.

[redacted] Clinic staff and subjects will be trained to assess and respond to situations regarding fluid balance as they may occur during treatments.

The target weight will be determined by the clinician through a careful physical exam, a focused history for symptoms of recent volume overload or volume depletion, and a review of previous dialysis sessions. [redacted]

[redacted] If the subject is more than 1kg above or below the target weight, the site will obtain the reason/narrative for this discordance. Possible reasons may include output not accounted for, oral intake not accounted for in the UF goal, improper weighing techniques, or unknown. Sites will discuss and document these responses with the subjects during their regular communications and transcribe a reason or reasons for the discordance in the applicable eCRFs as appropriate.

7.8 Control of Serum Phosphorus and Serum Potassium

Investigators will receive a notification per subject from the central laboratory for any of the following results:

- Any post-dialysis serum phosphorus level >5.5 mg/dL
- Any post-dialysis serum phosphorus level <2.2 mg/dL
- Any post-dialysis serum potassium level of <3.5 meq/L
- Any post-dialysis serum potassium level of >5.9 meq/L

Investigators will be instructed to follow up with their subjects regarding the specific result if clinically significant and treat the subject per their local standard of care guidelines. Investigators should also report any AEs (if applicable) using the guidance listed in Section 8. Additionally, investigators/designees will document what action was taken (if necessary) to address any alert values.

7.10 Clinical Observations

Each time a subject is dialyzed with HemoCare™ Hemodialysis System, the following information will be obtained from HemoCare™ Connectivity Platform Treatment Flowsheet (Section 7.11):

- Medications given during or immediately after treatment
- Anticoagulation regimen
- Treatment interventions
- Patient weight: pre- and post-dialysis (if unable to enter post-dialysis weight in device, subject will note the weight on the Treatment Flowsheet)
- Blood pressure: both pre and post-dialysis seated, or both pre-dialysis and post-dialysis standing
- Pulse: both pre-dialysis and post-dialysis seated, or both pre-dialysis and post-dialysis standing
- Body temperature: pre- and post-dialysis

A study nurse or their designee will collect study data weekly (minimum) as detailed in the section below. The Investigator or designee will assess each subject on a weekly basis according to care plan (see Section 7.11). The assessment may include blood pressure, fluid status, and dialysis prescription.

7.11 Treatment Flowsheet and Weekly Assessment

At every treatment with HemoCare™ Hemodialysis System (excluding In-Facility Introduction Period), subjects will complete Treatment Flowsheet to document certain data. In addition, the Investigator or designee will perform a weekly assessment of each enrolled subject. Sites may choose to communicate more frequently with the study subjects per local requirements or standard-

of-care. At a minimum, the Investigator or qualified designee must communicate with the subject weekly to review and discuss the following:

- Subject status/condition updates – potential AEs experienced
- Treatment interruptions
- Confirmation if the subject contacted the dialysis center for support with a device or health related issue
- Confirmation if the subject was able to sleep during treatment and duration of sleep
- Treatment outcome
- Confirmation if the subject altered their treatment parameters within the range(s) allowed by their Investigator
- Ultrafiltration details – unaccounted for output or oral intake
- Document completion of study requirements (e.g., PROs).
- Any changes to current medications, including those taken since the last Weekly Assessment
- Current treatment inventory needs, including any components with expiration dates coming up

The site staff will use this data along with the HemoCare™ Connectivity Platform treatment data to monitor the subject. This data will serve as supplemental source documentation for the sites to support consistent data collection during Evaluable Periods.

Sites may choose to communicate more frequently with the study subjects per local requirements or standard-of-care. At a minimum, the Investigator or qualified designee must communicate with the subject weekly to review. Based on all data collected from the subject, the site staff will complete their source logs and eCRFs as appropriate. [redacted] ll prescription changes will be documented in source documents.

7.12 Water and Dialysate Sampling Analysis

HemoCare™ Water Device shall not produce water that exceeds the chemical contaminant levels as stated in the ANSI/AAMI 13959:2014 standard. [redacted]

The Sponsor or its designee will train the person(s) responsible for collecting the water and dialysate samples during the study. Instructions will be provided in the study training materials. Standardized recovery methods and positive and negative controls will be incorporated into the testing protocol(s). A central laboratory will be used for all water and dialysate testing.

Sample results will be sent to the study sites and Sponsor for real time review and action (if appropriate). Observations and decisions regarding corrective measures (e.g., re-culture, consumables replacement, and/or disinfection of either device) will be based on the organism

[redacted]

growing, whether or not bacterial or endotoxin levels exceed the specified guidelines, and any clinical symptoms the subject may have. A Safety Management Committee will also review study wide results per the Safety Management Plan to search for trends and to action appropriately.

Analysis of water and dialysate will be performed on samples obtained as follows.

7.12.1 Chemical Contaminants –Tap Water

Samples of tap water will be collected by Sponsor or designees and tested for chemical contaminants from each study site during site feasibility, prior to HemoCare™ Hemodialysis System installations at the site. Samples will also be collected during home assessments, prior to device installation, while consented trial subjects are in the screening period. Source water needs to be of US EPA drinking water quality.

Additional tap water samples will be collected and tested from all actively participating locations, at a minimum, yearly or as required by site policy or local regulations. Excluding yearly retesting, trial subjects cannot treat on HemoCare™ Hemodialysis Systems in these locations until the results are received and reviewed by the trial site and Sponsor.

7.12.2 Chemical Contaminants – HemoCare™ Hemodialysis System

Post ultrafilter samples from HemoCare™ Hemodialysis System [redacted] will be collected from each device by sponsor personnel or designees upon installation, both at the study site and at the trial subjects' homes, and tested for chemical contaminants. [redacted] Trial subjects cannot treat on HemoCare™ Hemodialysis System in either location until the results are received and reviewed by the trial site and Sponsor.

Post ultrafilter water samples shall not exceed chemical contaminant levels as stated in the ANSI/AAMI 13959:2014 standard for dialysis water.

7.12.3 Microbiological Cultures – Incoming Source/Feed Water

Incoming source/feed water will be collected by sponsor personnel or designees at site assessment or installation, both in-center and at the trial subjects' homes, and tested for microbial levels.

These samples will be collected from the incoming source/feed water. Trial subjects cannot treat on HemoCare™ Hemodialysis System in these locations until the results are received and reviewed by the trial site and Sponsor.

Source water needs to be < 500 CFU/mL for microbial levels.

[redacted]

7.12.4 Microbiological Cultures and Endotoxin – Ultrapure Water or Dialysate

Ultrapure, post ultrafilter samples from HemoCare™ Hemodialysis System (water or dialysate) will be collected from the device by sponsor personnel or designees at installation, both in-center and at the trial subjects' homes, and tested for microbiological and endotoxin levels. At each sample collection time point, 2 ultrapure samples will be collected. Both samples will be collected and packaged using aseptic techniques, sent to the central lab for analysis, and analyzed independently, but concurrently.

[redacted] rial subjects cannot treat on HemoCare™ Hemodialysis System in these locations until the results are received and reviewed by the trial site and Sponsor.

If subsequent in-center installations are required (e.g., after initial device installation is complete, a second device is installed at the same clinic), new ultrapure installation samples will be collected. The subject cannot treat on the newly installed device until the results are analyzed and reported. Once a HemoCare™ Hemodialysis System has been installed and passes the ultrapure microbial and endotoxin analysis, any replacement device (e.g. replacement treatment device or water device) will not require ultrapure samples to be recollected unless source water has changed.

[redacted]

Ultrapure samples (water or dialysate) produced by HemoCare™ Hemodialysis System shall not exceed microbial or endotoxin levels as stated in the ANSI/AAMI/ISO 23500-5:2019 standard. Based on this standard, the acceptable limit for microorganisms is < 0.1 CFU/mL and the acceptable limit for endotoxin is < 0.03 EU/mL

[redacted]

[redacted]

7.12.6 Process for Responding to Out-of-Specification Results

7.12.6.1 Decision Tree

Clinical study decision trees for ultrapure [redacted] have been developed and will be provided to study sites. These decision trees provide guidance to the clinical site and the DEKA R&D Corp. and CVS Kidney Care team on appropriate actions to be taken in situations where out-of-specification (OOS) results are received from ultrapure [redacted]

Upon confirmation of an OOS value for either endotoxin or bacteria, the user will be directed to replace the consumable portions of the device [redacted]

Additional actions may include:

- All device logs evaluated for anomalies
- Aseptic procedure checklists recorded during sample collection and processing reviewed for anomalies
- Contract Laboratory will conduct an investigation of their procedures and processes for any OOS endotoxin or micro-organism result
- Consideration for additional actions such as retrieval and analysis of hardware and/or disposables, on site investigation for additional machine and environmental cultures, etc.

[redacted]

[redacted]

[redacted]

[redacted]

7.12.6.3 Endotoxin Out-of-Specification Analysis – Ultrapure [redacted]

[redacted]

After an OOS value is recorded on the first aliquot volume tested from the primary tube, a test will be performed on a second aliquot that will be independently diluted, to eliminate any contamination that might have been introduced during the first aliquot dilution step. If this retest confirms an OOS value, the root cause investigation will continue to identify a probable cause of the endotoxin. The Secondary Tube will be assayed as part of the root cause investigation.

7.12.7 Chloramine, pH, and Conductivity Testing

Chloramine testing of the water for dialysis will be done prior to each dialysis treatment.

[redacted]

[redacted]

[redacted]

8 Adverse Events reporting

An AE is any untoward medical occurrence in a subject administered by a study product and which does not necessarily have a causal relationship with the treatment or study product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory function), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., bacteremia, pancreatitis, etc.) or outcome of death temporally associated with the use of the study product, whether or not the event is considered to have a causal relationship with the study product.

Laboratory and vital sign abnormalities qualify as AEs if medical intervention is required to treat or address the abnormality, if the subject must be discontinued from the study due to the abnormality, or if the value exceeds specific limits defined by the protocol as qualifying it as an AE.

[redacted]

An elective procedure/surgery that occurs during the course of a study, but is being performed for a documented pre-existing condition and was pre-planned prior to study entry will not qualify as an AE. If, however, the pre-existing condition unexpectedly deteriorates during the study requiring the procedure/surgery to be performed earlier than planned, the condition for which the procedure/surgery is being performed will qualify as an AE.

Adverse events will be collected starting from the time of enrollment until the end of participation in the study. If an AE occurs, a full description of the event should be recorded including the date of onset, severity, time course, description, actions taken, and causal relationship of the AE to the study product(s). Investigators should review and reference the Causality definitions below when determining relationship of the AE to the study product. The investigators may also discuss the event(s) with the Medical Monitor, but the Investigator must make, document and report the relationship for every AE. All AEs must be documented in source documents and on the eCRFs, no matter how common they are for a particular subject and regardless of the causality assigned by the Investigator.

The process for the collection of subject reported events will be the same for both Evaluable Treatment periods. Raw events will be collected through the Weekly Assessments, as well as routine medical record review and standard of care communications with the subject and/or care partner.

All AEs and SAEs, regardless of relatedness, should be recorded.

Additionally, any AE voluntarily reported by the subject should be recorded and verified by the Investigator or designee on the appropriate source documents and eCRF pages.

The outcome/resolution of all AEs and SAEs will be determined by the Investigator and documented on the AE eCRF. Investigators will be instructed to follow all AEs/SAEs as follows: Unrelated AEs will be followed until resolution or until the end of the study whichever occurs first. Adverse device effects (related AEs) and all SAEs (related or not) will be followed until resolution or stable, including following the subject after the end of the study if necessary. The outcome categories that can be chosen on the eCRF by the Investigator include: Fatal, not recovered/not resolved (this outcome is reached for AEs which are ongoing when the subject's end of study is due to death related to another AE), Recovering/Resolving (this outcome is reached for AEs which are ongoing at the subject's end of study), Recovered/Resolved with Sequelae (if there are some residual effects caused by the event), Recovered/Resolved, and Unknown.

All SAEs regardless of their relationship to the study product will be submitted to Sponsor or designee by the Investigator or designee within 24 hours of becoming aware of the event. If an investigator becomes aware after study completion of an SAE that occurred in a subject during their participation in the study, the SAE must be reported on the SAE Form within 24 hours after awareness. Serious adverse events occurring within 30 days of study completion (per subject) will also be reported.

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

8.1.1 Definitions of Adverse Event Terms

Study Product: For this protocol, the term "study product" is synonymous with IP

Date of Onset: The date that the signs and symptoms or diagnosis of the AE began

Severity: Severity will be assessed for each AE and defined using the following criteria:

Mild – Is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level. The AE resolves spontaneously or may require minimal therapeutic intervention.

Moderate – Produces limited impairment of function and can require therapeutic intervention, but produces no sequelae.

Severe – Results in a marked impairment of function and can lead to temporary inability to resume usual life pattern. The AE produces sequelae requiring (prolonged) therapeutic intervention.

Causality: Causality Assessment – A determination is made by the Investigator and sponsor as to whether there is a reasonable possibility that the device or drug is etiologically related to/associated with the AE.

Causality assessment includes, for example, assessment of temporal relationships, association (or lack of association) with underlying disease, treatment association (or lack of association), presence (or absence) of a more likely cause, and physiologic plausibility. Categories for causality assessment are "related," "possibly related," "unlikely related" and "not related."

Related: An AE follows a strong temporal relationship to the device or drug, and another etiology is unlikely or significantly less likely.

Possibly Related: An AE follows a reasonable temporal relationship to the device or drug, and an alternative etiology is equally or less likely compared to the potential relationship to the device or drug.

Unlikely Related: An AE has little or no temporal relationship to the device or drug and/or a more likely alternative etiology exists.

[redacted]

Not Related: An AE that is due to underlying or concurrent illness, complications, concurrent treatments or effect of another concurrent drug/therapy and is not associated to the device or drug (i.e. does not follow a reasonable temporal relationship to the use of the device or drug, or has a much more likely alternative etiology).

8.1.2 Serious Adverse Events

The following criteria qualify an AE as an SAE:

Death:	An event resulting in death (including a fetal death).
Life-threatening:	In the opinion of the Investigator, an event that would have resulted in immediate death if medical intervention had not been undertaken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event resulting in inpatient admission of the subject to the hospital. (Note: Inpatient hospitalization refers to any inpatient admission, regardless of length of stay). Visits to the emergency room or outpatient facility do not constitute hospitalization for the purpose of the definition.
Prolongation of Hospitalization:	An event that prolongs the subject's stay in the hospital. By definition, this is a different event from the event that resulted in the hospitalization.
Congenital Abnormality:	An abnormality detected at or after birth in the offspring of a study subject.
Persistent or Significant Disability/Incapacity:	An event that substantially interferes with the subject's daily activities of living. This category is not intended to include events of relatively minor medical significance such as minor trauma, diarrhea, nausea, etc.
Important Medical Event:	A medically important event or reaction that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or requires intervention to prevent one of the other outcomes listed above. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse.

8.1.3 Adverse Drug/Device Reaction

All noxious and unintended responses to a medicinal product that are related to any dose should be considered adverse drug reactions (ADR). The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

[redacted]

8.1.4 Unexpected Adverse Drug/Device Reaction

An unexpected ADR is an adverse reaction for which the nature or severity is not consistent with the applicable product information.

8.1.5 Suspected Unexpected Serious Adverse Reaction

An AE suspected to have a causal relationship to an investigational or marketed drug/device and meeting criteria for seriousness and unexpectedness. Suspected unexpected serious adverse reactions (SUSARs) are also reportable for active comparator products, placebo, or the clinical study protocol itself (i.e. events due to study procedures).

8.1.6 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.1.7 Adverse Events Related to Hemodialysis Therapy (Anticipated Adverse Events)

The following are common adverse reactions (signs, symptoms and diagnoses) that have been reported related to HD therapy: hypotension; hypertension; muscle cramps; nausea; vomiting; headache; chest pain; back pain; itching; fever; chills; disequilibrium syndrome; hypersensitivity (allergic) reactions including asthmatic reactions, respiratory arrest, pruritus, urticaria, erythema, and peripheral and facial edema; hypovolemia; hypervolemia; cardiac arrhythmia; cardiac tamponade; intracranial bleeding; seizures; hemolysis; air embolism including micro-air embolism; blood loss; infection; access related problems including infiltration; abdominal pain; fluid overload; hematuria; bleeding; and electrolyte imbalance. Definitions of these adverse reactions are provided in Appendix 1.

8.1.8 Microbiological-Associated Adverse Events

If a failed water sample is accompanied by AEs such as fever, rigors or sepsis within 4 hours after a HD treatment, the event will be considered a microbiological-associated AE(s). The events will be documented on the AE eCRF; the positive culture results will be documented on a Product Issue Form.

[redacted]

A failed dialysate sample from a device actively treating a subject will always be considered a microbiological-associated AE, regardless of whether accompanied by symptoms. The events will be documented on an AE eCRF; the positive culture results will be documented on a Product Issue Form eCRF.

8.1.9 Performing Adverse Events Assessments

The AE collection period for each subject starts with enrollment and completes when the subject ends the study. During the course of the study, the Investigator or designee shall routinely monitor each subject for the occurrence of any AE. Routine monitoring should include regular communication with the trial subject, review of laboratory results, assessment of anticoagulation, dialysis access, medication use, and by reviewing the treatment details in the HemoCare's™ Connectivity Platform as reported by the assigned HemoCare™ Hemodialysis System. Site team members should follow up and gather additional details from subjects when appropriate based on these information sources as well other data sources including but not limited to physical exams, vital signs, subject questionnaires, and concomitant medication listings.

In addition to AE collection, study sites should discuss the AE reporting process with their study subjects and encourage them to volunteer the applicable information to the appropriate site team members in real time. All site team members should likewise monitor and gather information from subjects if an event is suspected based on subject conversations or data points collected. This level of open dialog should drive the AE collection and reporting process.

During the course of the study, controls will also be in place to consistently solicit AE information during the Weekly Assessments. The site team members will use their clinical judgment to follow up with the subjects and report any applicable event(s).

During these periods the site Investigator or designee is required to contact the subject weekly to discuss their current status, treatment, and condition. These timelines are minimum requirements for the sites to follow, they should follow their local guidelines if more frequent communication is required (e.g., local standard of care or to follow up on current/recent events).

8.2 Adverse Event Reporting

8.2.1 Reporting Adverse Events to Sponsor/Designee

During the course of the study, the Investigator or designee will routinely monitor each subject for the occurrence of any AE/ADE. If an AE/ADE occurs, the Investigator or designee will complete the AE eCRF which includes the following:

- Description of the event
- Start and stop date of the event
- Timing of the event (prior to first study treatment, during treatment set-up, during treatment, within 4 hours after treatment ends, > 4 hours after treatment ends)

- Seriousness of the event (yes, no) (assessed by PI or Sub-I)
- Severity of the event (mild, moderate, or severe) (assessed by PI or Sub-I)
- Causality of the event (related to treatment and/or related to the device) (assessed by PI or Sub-I)
- Action taken
- Outcome of the event (fatal, not recovered/not resolved, recovered/resolved with sequelae, recovered/resolved, and unknown)

All SAEs must be reported to the Sponsor/designee within 24 hours of the Investigator or designee becoming aware of its occurrence. The informed site team member should also contact their site monitor by phone or email to notify him/her of the event. This requirement is irrespective of whether the AE is thought to be possibly related to the study product or not. Expedited Reporting of Serious Adverse Events and Suspected Unexpected Serious Adverse Reaction (SUSAR). Sponsor/designee will assess each SAE reported by the Investigator to determine if the SAE qualifies as an expedited report according to FDA criteria. Sponsor/designee will report to FDA according to the applicable time requirements.

Per regulations, when an Unexpected Adverse Device Effect (UADE) or SUSAR occurs Investigators will receive a letter from Sponsor/designee describing the UADE/SUSAR. The Investigator should file this letter within their Investigator Study Binder. Additionally, the expedited report letter should be submitted by the Investigator to their IRB/REB, as appropriate per FDA regulations.

8.2.2 Device-Related Product Complaints

All device-related complaints [redacted] will be collected [redacted]

8.2.3 Trial Subject Reporting – Product Issues

Throughout the trial, HemoCare™ Hemodialysis System will record and report device alarms. The alarm time(s), code(s), and description(s) will be reported to the Sponsor as

[redacted]

they occur via HemoCare™ Connectivity Platform. This data will be maintained for end of study statistical analysis. Additionally, this data will be reviewed and trended by the Sponsor and/or designee for safety concerns or service requirements. In addition to device reported product issues, trial sites will also report product issues.

During both Evaluable Periods (Assisted & Unassisted), trial subjects or care partners will be instructed to contact the on-call study site staff for any product issues which cannot be resolved using the User Manual or training tools. The site staff will assist the subject in resolving the product issue using the device User Manual and training material. If the site is unable to resolve the product issue, they will be instructed to contact the Sponsor/designee for device support. The site staff will also contact the Investigator or designee to discuss next steps for the trial subject in the event of an incomplete or missed treatment.

[redacted]

8.3 Clinical Laboratory Tests

8.3.1 Laboratory Parameters

A central laboratory will perform laboratory tests for hematology and serum chemistries.

With exception, sites may use and will be encouraged to use their local laboratory for activated partial thromboplastin time (aPTT) measurements if using the central laboratory may confound results based on the potential shipping timelines (e.g., local weather, sample collection time point).

Subjects will be in a seated or supine position during blood collection. List of clinical laboratory tests is found below.

List of Laboratory Tests:

Serum Chemistry:

- Comprehensive metabolic panel (including glucose, calcium, sodium, potassium, total carbon dioxide or serum bicarbonate, chloride, urea, creatinine, ALP, ALT, AST, total bilirubin, serum albumin, and total protein + serum phosphorous (pre-dialysis))
- Iron profile (pre-dialysis)

Hematology:

- CBC (pre-dialysis)

Coagulation:

- Activated partial thromboplastin time (aPTT)

[redacted]

CBC=complete blood count; ALP=alkaline phosphatase; ALT=alanine amino transferase; AST=aspartate amino transferase; aPTT=activated partial thromboplastin time

The Investigator will receive the laboratory results for review and signature. The Investigator will be notified of any laboratory value that is outside of the normal range, as defined by the central laboratory and included as part of the laboratory manual. If a clinically meaningful 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.

8.3.2 Sample Collection, Storage and Shipping

A study specific Laboratory Manual will be provided by the central laboratory to the Investigators and will include detailed instructions on the collection, preparation, storage, and shipping procedures for blood samples and the appropriate laboratory ranges. If a local laboratory is used for aPTT testing, the local laboratory will be required to provide kits and instructions to Investigators.

Depending on site staff availability, an in-home nurse or technician service may be utilized to collect, process, and ship samples which must be collected during the home period. The in-home nurses selected for this activity will be qualified in sample collection, processing, packaging, and shipping. Use of in-home nurses will minimize sampling errors and maximize consistency. During the in-center periods, the sites will be required to provide qualified nurses for sample collection, processing, packaging, and shipping.

9 Statistical Considerations

9.1 General Considerations

Further details of the planned statistical methods presented below will be provided in the study statistical analysis plan (SAP). The purpose of the SAP is to further elaborate the statistical methods described in the protocol and describe analysis conventions to guide the statistical programming work. Any changes to the final SAP will be documented. Unless otherwise specified, treatment effects will be evaluated based on a 2-sided significance level of 0.050 (when rounded to 3 decimal places)

9.2 Determination of Sample Size

The goal is to have at least 1000 HemoCare™ treatments in both Evaluable Periods, in agreement with the FDA, to make a *clinical determination* of the safety of HemoCare™ based on the rate and type (i.e., device related) of AEs documented. To achieve this goal, at least 30 subjects will enter the Assisted Evaluable Period. No more than 25% of the total study subjects who complete the study may be enrolled at one site. Assuming each Evaluable Period is 3.5 treatments per week (one treatment every other night), each patient is expected to contribute 34 treatments to each Evaluable Period and 68 evaluable treatments to the study. [redacted]

[redacted]

[redacted]

Based upon the number of treatments and the expected rate of adverse events, the current study design is under-powered to detect a clinically meaningful (less than 10%) non-inferiority margin for the Unassisted Evaluable Period.

For the primary performance endpoint, 'success' is defined as a subject who has all stdKt/Vurea measures in an evaluable period greater than or equal to 2.0. Several sets of simulation samples were generated (2,000 samples per set) assuming a rate of success between 95% and 99.5% for the Assisted Evaluable Period treatments paired with some fewer successes for the Unassisted Evaluable Period treatments. The success rate of the 2 periods were compared and the CI interval for the differences were calculated. With 30 subjects in each Evaluable Period, a margin of 10% will provide 91% power to declare non-inferiority if the actual success rate is 99% and 83% power if the actual success rate is 98%.

9.3 Analysis Populations

The Per Protocol (PP) population will include all subjects and subject data that meets the following criteria specified below:

1. Each subject must not have any enrollment violations defined as failure to meet one or more inclusion criteria or meeting one or more exclusion criteria.
2. Each subject must receive at least 34 treatments with HemoCare™ in each evaluable study period. All treatments that are initiated with HemoCare™ will be counted regardless of the length of the dialysis session.
3. For subjects who meet criteria 1 and 2 above, all adverse events that occur in each Evaluable Period will be counted.

The PP population will be used for analyses of the primary safety endpoint and primary performance endpoint.

The Intent-to-Treat (ITT) population will include all subjects who have used the HemoCare™ at least once during the Assisted Evaluable Period.

Poolability of the data will be examined by assessing the heterogeneity of the primary endpoint results across sites with 5 or more subjects enrolled.

9.4 Primary Endpoints

9.4.1 Primary Safety Endpoint

The primary safety analysis will be to compare the Unassisted Home Evaluable Period AE rate per 100 HemoCare™ Hemodialysis System treatments against the Assisted Evaluable Period AE rate per 100 HemoCare™ Hemodialysis System treatments. A two-sided 90%

[redacted]

CI will be generated for the rate ratio (λ_2/λ_1) comparing the relative difference in AEs for the two scenarios using a negative binomial regression model. The analysis will be carried out on the ITT population. The response variable is the total number of AEs. The model will include an indicator variable that is equal to one if treatment is "Assisted Evaluable Period" and zero otherwise. In addition, the log of the number of treatments will be included as an offset variable in the model and a subject specific random effect for treatment period will be included with covariance structure specified as "unstructured."

Let $\lambda_i = \frac{n_{aei}}{N_{txi}}$ be the rate of adverse event during treatment $i = \begin{cases} a\ for\ assisted\ treatment \\ u\ for\ unassisted\ trreatment \end{cases}$

Where:

$n_{aei} = Number\ of\ adverse\ event\ \ during\ treatment\ i, and$
$N_{txi} = Number\ of\ treatment\ type\ i$

Given a non-inferiority margin δ,

$$H_0: {}^{\lambda_u}/_{\lambda_a} > 1 + \delta$$
$$H_1: {}^{\lambda_u}/_{\lambda_a} \leq 1 + \delta$$

The Negative Binomial distribution will be used as a link function with the log transformation will be used to estimate the ratio and it's Confidence Interval. The logarithm of the Number of treatment for each treatment modality will be included as an offset term to account for any potential unpredicted unbalance between the two modalities sample sizes. If the Negative Binomial model fail to converge, the Poisson distribution with Scale =Dispersion will be adjusted.

Let UCI be upper boundary of the ${}^{\lambda_u}/_{\lambda_a}$ ratio confidence interval. H_0 is rejected if UCI $\leq 1 + \delta$ resulting in accepting H_1 and concluding Unassisted treatment are not inferior than assisted treatment.

The same analysis will be conducted using the PP population.

The evaluation of the primary safety endpoint will be based on the results from the ITT population and the PP population.

9.4.2 Primary Performance Endpoint

Performance of HemoCare™ Hemodialysis System will be assessed by weekly stdKt/V_{urea} that will be collected every two weeks during each Evaluable Period. A successful weekly stdKt/V_{urea} is defined as a value of at least 2.0. If there is a retest of stdKt/V_{urea} for a

[redacted]

particular week (e.g., a missed or damaged sample) then the retested value will be used for analysis.

During each Evaluable Period, a binary outcome variable will be defined to be 1 if the weekly stdKt/V_{urea} for a given week meets the success criteria and 0 otherwise. For each subject, this will result in approximately 5 binary outcome values for each period. Each subject will be considered as meeting the primary performance endpoint for that period if all weekly stdKt/V_{urea} values meet the performance success criterion. A Non-inferiority test will be conducted. The difference in proportion of subjects (P_1-P_2) meeting the performance criteria in the Unassisted Evaluation Period (P_2) and the Assisted Evaluation Period (P_1) will be reported with a two-sided 90% CI.

$$H_0\colon\ p_1 - p_2 \geq \delta$$
$$H_1\colon\ p_1 - p_2 < \delta$$

If the upper bound of the Confident interval is less than δ=0.10 then the null Hypothesis is rejected and non-inferiority is demonstrated.

The analysis will be carried out on the PP population. In addition, an analysis using the ITT population and the impact of missing data on the PP analysis will be explored as sensitivity analyses.

Multiple imputation (MI) will be used to assess the sensitivity of missing data on the ITT population. A MI logistic regression model for the efficacy success of each treatment-week will include the following factors: treatment, age, site, and weeks on home dialysis.

A risk difference analysis with continuity correction for independent samples will be performed. Although this will be paired rates, the independent sample analysis will be conducted because it is highly expected not having any failure, at least on the assisted treatment evaluable period.

The same analysis will be conducted using the PP population.

Furthermore, the impact of missing data on the primary analysis, will be explored as sensitivity analysis for both, ITT and PP population.

The evaluation of the primary performance endpoint will be based on the results from the PP population and the ITT population.

9.5 Secondary Endpoints

1. Adverse events will be mapped to a primary MedDRA System Organ Class (SOC) and Preferred Term (PT). Anticipated AEs and SAEs and unanticipated AEs and SAEs will be summarized during each Evaluable Period by SOC and PT. In addition, all device-

[redacted]

related AEs and SAEs will be summarized during each Evaluable Period by SOC and PT.

An overview of the total number of AEs and SAEs (anticipated, unanticipated, and device-related) during each Evaluable Period will be provided. In addition, for each Evaluable Period an overview will be provided of the total number of subjects having at least 1:

- Anticipated AE
- Anticipated SAE
- Unanticipated AE
- Unanticipated SAE
- Device-related AE
- Device-related SAE

The proportion of subjects having at least one AE within each of these six AE subgroups will be compared between Evaluable Periods with exact McNemar's tests.
For each of these six AE subgroups the hypotheses will be:

H_0: $P_u = P_a$
H_a: $P_u \neq P_a$

Where P_u = Proportion of subject having at least 1 event during unassisted treatments and P_a is the proportion of subjects having at least 1 event during the Assisted treatments.

Identifying the number of subjects who had at least 1 event during assisted treatment and no event during unassisted treatment as n_{12}, and subjects who have no event during assisted treatment and at least 1 event during unassisted treatment as n_{21}, the indicator $Q = {(n_{12} - n_{21})^2}/{(n_{12} + n_{21})}$ will be compared to x^2 with 1 Degree of Freedom if $(n_{12} + n_{21}) > 20$. Otherwise the correction $Q = {(|n_{12} - n_{21}| - 1)^2}/{(n_{12} + n_{21})}$ will be used. The Null Hypothesis will be rejected if the P-value for the x^2 is less than 0.10.

No multiplicity adjustment will be done for these secondary endpoints.

Furthermore, the proportion of subjects having AEs within each of these six AE subgroups will be summarized by SOC, PT and severity (mild, moderate or severe) during each Evaluable Period for the most severe rating of each AE per subject.

2. The incidence of decreased serum phosphorus defined as at least 1 post-dialysis serum phosphorus level < 2.2 mg/dL, the incidence of elevated serum phosphorous defined as a least 1 post-dialysis serum phosphorus level > 5.5 mg/dL, will each be compared between Evaluable Periods with exact McNemar's tests.

[redacted]

3. The incidence of decreased serum potassium defined as at least 1 post-dialysis serum potassium level of < 3.5 meq/L, and the incidence of elevated serum potassium defined as at least 1 post-dialysis serum potassium level of > 5.9 meq/L, will each be compared between Evaluable Periods with exact McNemar's tests.

4. A descriptive summary of UF and target weight during each evaluable period will be provided.

[redacted]

9.7 Handling of Missing Data

Sensitivity analyses of the primary safety endpoint and primary performance endpoint will be done using methods for single imputations and multiple imputations (MI) for the ITT population and the PP population.

9.7.1 Device Holiday

A Device Holiday is defined as a period of time where a subject is unable to or does not perform treatments on the HemoCare™ Hemodialysis System per the prescribed schedule. A Device Holiday may result in the extension of a subject's participation in the study in order to receive the required number of treatments in a given period. Any time a patient is not able to treat at home, they will return to their training facility or another in-center facility as determined by the site Principal Investigator.

Reasons for a Device Holiday are inclusive of, but not limited to:

- Subject hospitalization
- Missed treatment
- Required device servicing

[redacted]

- Boil-water advisory/order

9.8 Other Assessments or Analysis

Subgroup analysis may be performed using for example subgroups defined from age (below 55 years versus 55 years or more), diabetes status (diabetic versus non- diabetic). Where applicable, the potential difference within a subgroup may also be investigated in the regression model by including the subgroup as covariate in the model.

For primary safety endpoint, a potential time trend during each Evaluable Period will be investigated by including the time since start of the Evaluable Period in the model.

Details regarding further AE analyses, as well as other assessments or analyses are included in the SAP.

9.9 Interim Analysis

An interim analysis is not planned for this study

10 Data Management, Quality Control and Quality Assurance

10.1 Clinical Database

The designated CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures (SOPs) of the data management and biostatistics departments of sponsor or the designated CRO.

Study centers will enter data directly into an EDC system by completing the CRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

[redacted]

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and WHO Drug for medications.

[redacted]

Missing or inconsistent data will be queried in writing to the Investigator for clarification. Subsequent modifications to the database will be documented

10.2 Audits and Inspections

In addition to the routine monitoring procedures and in accordance with Good Clinical Practice (GCP) principles, GCP audits might well be performed by the Quality Assurance members of Sponsor/Designee.

These audits of clinical research activities are in accordance with applicable regulatory requirements, Sponsor/designee internal policies and procedures, to evaluate compliance with the principles of GCP. A Regulatory Authority may also wish to conduct an inspection (during the study or even after its completion). If a Regulatory Authority requests an inspection, the Investigator must immediately inform the Study Monitor of Sponsor/designee that this request has been made.

11 Administrative Considerations

11.1 Institutional Review Board or Research Ethics Board Approval

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

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

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

Sites must adhere to all requirements stipulated by their respective IRB/REB. The Investigator will promptly notify their IRB/REB of any planned protocol amendment and will not implement any protocol amendment until the IRB/REB has provided written approval of, or written favorable opinion on, the amendment.

[redacted]

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Edinburgh 2000), the ethical and quality standards of good clinical practice (ICH E6) and all applicable regulatory requirements and laws. The PI will provide all necessary information on the protocol and the study device to all physicians, nurses, and other personnel who participate in this study under the PI's supervision and will discuss this material with them as needed, to ensure that they are fully informed regarding the conduct of the study and the potential effects of the study device.

11.3 Compliance with Protocol and Protocol Amendments

The Investigator, and all physicians, nurses, and other personnel who participate in this study under the Investigator's supervision, will conduct the study according to the currently approved version of the protocol. In cases where the protocol is not followed, the site staff will document the reason for the deviation from the protocol and any corrective actions taken and/or preventative measures put in place to avoid future occurrences. Serious or repeated deviations from the protocol will result in termination of the Investigator's participation in the study.

Neither the Investigator, nor the sponsor, will amend or modify the protocol without notifying the other. Any protocol amendment must be approved by DEKA R&D Corp. and CVS Kidney Care, in writing, must be agreed to by the Investigator in writing, and must be approved by the Investigator's IRB/REB in writing prior to implementation of the amendment.

11.4 Subject Information and Consent

The nature of the study will be fully explained to each potential subject and care partner and voluntary, written (signed and dated) informed consent will be obtained from the subject and care partner prior to enrolling the subject in the study. No study-specific procedures will be performed prior to the Investigator or their designee obtaining written informed consent. [redacted]

Preparation of the ICF is the responsibility of the Sponsor/Designee and must include all elements required by GCP and applicable regulatory requirements and must adhere to GCPs and to the ethical principles that have their origin in the Declaration of Helsinki (see Appendix 2 for the requirements of an informed consent statement). All ICFs must be reviewed by the Sponsor prior to IRB/REB submission. Only subjects with the initial intention to complete the study should be considered for entry into the study.

The PI must provide the subject/care partner or a legal representative with a copy of each ICF and written information about the study in English only. The language must be nontechnical and easily understood. The PI should allow the time necessary for the subject or the subject's legal representative to inquire about the details of the study after which the ICF must be signed and

[redacted]

personally dated by the subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or a legal representative should receive a copy of the signed ICF and any other written information provided to the study subject prior to the subject's participation in the trial. The PI must furnish the Sponsor or its designee with a copy of each IRB/REB-approved ICF to be used in this study prior to the commencement of the study.

11.5 Subject Confidentiality

All subject information, medical records, and laboratory data will be kept confidential.

Information and data may be discussed, analyzed, and reported; however, code numbers will identify the subject on the eCRFs and in any reports, and the subject's identity will be kept confidential.

[redacted]

11.6 Protocol Violations/Deviations

Protocol violations/deviations will be documented in source for transmission into a tracking system. The clinical team will review deviations at a study level on a regular basis for issues and resolution.

11.7 Access to Source Documentation

Monitoring visits will occur at regularly scheduled intervals at the investigational site to allow for verification of source documents and comparison of source data with the information recorded on the eCRFs.

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

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

If an onsite visit is not possible due to public health or patient safety concerns, the site must provide electronic copies of source documentation to enable a remote monitoring visit, to ensure continued review of data quality and integrity of the study. The Sponsor or designee will work with the site

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to enable this according to all federal, local, and institutional Patient Health Information protective measures.

This study may be subject to an independent audit at the investigational site, which will be conducted by independent auditors. Full consultation with appropriate personnel will be made prior to and during such audit. The PI must be available during the audit. If the PI is contacted by any regulatory authority regarding an audit for this study or any other study, the PI will contact the Study Manager and Medical Monitor immediately.

11.8 Retention of Data

The PI must retain all study records including IP disposition records, and source documents (including informed consent documents, safety reports, etc.) for the maximum period required by applicable regulations and guidelines or institution procedures or for the period specified by Sponsor, whichever is longer. The PI must contact the Sponsor before destroying any records associated with the study to determine disposition of records. The Sponsor or its designee will notify the PI when the trial records are no longer needed. If the PI withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another PI, IRB). Sponsor/designee will be notified in writing of any such transfer.

11.9 Publication and Disclosure Policy

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

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

12 References

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3. Culleton BF, Walsh M, Klarenbach SW, et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA*. 2007;298(11):1291-1299.
4. Rocco MV, Lockridge RS, Jr., Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: The Frequent Hemodialysis Network Nocturnal Trial. Kidney Int.2011;80(10):1080-1091.
5. Pauly RP, Gill JS, Rose CL, et al. Survival among nocturnal home hemodialysis patients compared to kidney transplant recipients. Nephrol Dial Transplant.2009;24(9):2915-2919.
6. Bernardo AA, Marbury TC, McFarlane PA, Pauly RP, Amdahl M, Demers J. Clinical safety and performance of VIVIA: a novel home hemodialysis system. Nephrol Dial Transplant (2016) 0: 1–8. doi: 10.1093/ndt/gfw044.

Appendix 1: Adverse Reactions Related to Hemodialysis Therapy

Hypotension: Decrease in systolic blood pressure of at least 20 mmHg in combination with symptoms such as nausea, vomiting, muscle cramps, dizziness, fainting. The reference value is the subject's own blood pressure taken pre-dialysis.

Disequilibrium Syndrome: Is an acute neurological complication of dialysis characterized by signs and symptoms restlessness, headache, nausea, vomiting, blurred vision, muscle twitching, tremor, disorientation, convulsions and coma.

The following definitions are obtained from Taber's Cyclopedic Medical Dictionary, 21st Edition unless otherwise indicated:

Fever: Abnormal elevation of temperature over patient's basal pre-dialysis temperature of $\geq 2°$ F or a temperature $\geq 100.5°$ F.

Muscle cramps: Painful involuntary contraction of muscles.

Nausea: An unpleasant queasy or wavelike sensation in the back of throat, epigastrium or abdomen that may or may not lead to the urge or need to vomit.

Vomiting: Ejection through the mouth of the contents of gastrointestinal tract.

Headache: Pain felt in the forehead, eyes, jaws, temples, scalp, skull, occiput, or neck.

Chest pain: Discomfort felt in the upper abdomen, thorax, neck, or shoulders.

Back pain: Pain (discomfort) felt in or along the spine or musculature of the posterior thorax. It is usually characterized by dull, continuous pain and tenderness in the muscles or their attachments in the lower lumbar, lumbosacral, or sacroiliac regions.

Itching: Pruritus; a generally unpleasant sensation in the skin that creates the urge to rub or scratch it.

Chills: Involuntary, rapid contractions of muscle groups (shivering) accompanied by the sensation of cold, or the sensation of being cold without shivering.

Hypersensitivity (allergic) reactions: A reaction resulting from hypersensitivity to an antigen. This may include any of the following:

> Asthmatic reactions: A reaction caused by increased responsiveness of the tracheobronchial tree to various stimuli, which results in episodic narrowing and inflammation of the airways.

Respiratory arrest: Cessation of breathing resulting in life threatening or fatal event requiring respiratory support such as artificial ventilation.

Pruritus: Itch; a tingling or faintly burning skin sensation that prompts a person to rub or scratch.

Urticaria: An allergic reaction marked by multiple discrete swellings on the skin (wheals) that are intensely itchy and last up to 24 hours. The wheals appear primarily on the chest, back extremities, face, or scalp. Synonym: hives.

Erythema: Reddening of the skin.

Peripheral and facial edema: Body tissues in the face and extremities contain an excessive amount of tissue fluid in the interstitial spaces.

Hypovolemia: A decreased blood volume that may be caused by internal or external bleeding, fluid losses, or inadequate fluid intake.

Hypervolemia: An abnormal increase in the volume of blood circulation.

Cardiac arrhythmia: Any abnormal heart rhythm caused by physiological or pathological disturbances in the discharge of cardiac impulses from the sinoatrial node or their transmission through conductive tissue of the heart. The diagnosis is confirmed by electrocardiogram, Holter monitoring or electrophysiologic testing. This will include sinus bradycardia (heart rate <50 beats per minute), sinus tachycardia (>100 beats per minute), premature atrial beats, supraventricular tachycardias, atrial fibrillation, atrial flutter, multifocal atrial tachycardia, atrioventricular junctional rhythm, ventricular tachycardia, ventricular premature beats, ventricular fibrillation, accelerated idioventricular rhythm, long QT syndromes, sick sinus syndrome, second degree heart block, complete heart block, ventricular tachycardia and brady-tachy syndromes.

Cardiac tamponade: A life-threatening condition in which elevated pressures within the pericardium impair the filling of the heart during diastole. The diagnosis is confirmed by imaging study such as echocardiogram.

Intracranial bleeding: Blood emitted from an injured vessel within the cranium or skull. The diagnosis confirmed by imaging study such as CT scan or MRI.

Seizures: Convulsions or other clinically detectable events caused by a sudden discharge of electrical activity in the brain. New onset seizures confirmed by electroencephalogram (EEG).

Hemolysis: For hemodialysis subjects it is the destruction of red blood cells (RBCs) because of their exposure to: 1. Overheated dialysis solution, 2. Hypotonic dialysis solution (insufficient concentrate-to-water ratio), or 3. Dialysis solution contaminated with formaldehyde, bleach, chloramines (from city water supply), copper (from copper piping), fluoride, nitrates (from water supply), zinc, or hydrogen peroxide. Blood line obstruction/narrowing may also be a cause. Symptoms are non-specific and may include nausea, vomiting, chest pain, abdominal pain, shortness of breath and hypotension. Laboratory confirmation of hemolysis as increased in free plasma hemoglobin level and increased serum lactate dehydrogenase.

Air embolism/Micro-air embolism: Obstruction of a blood vessel caused by an air bubble. For hemodialysis subjects, this can occur when air enters through an arterial needle, pre-pump arterial tubing segment or an inadvertently opened end of a central venous catheter.

Blood loss: Loss of blood during a hemodialysis treatment usually created by clotting or disconnect/leak within the extracorporeal circuit.

Infection: A disease caused by microorganisms, especially those that release toxins or invade body tissues. The diagnosis confirmed by bacteriological culture of the infected site as in an access or blood cultures for systemic infection.

Access related problems:

Infiltration: Dysfunction of the subject's vascular access which includes dislocation of the vascular access device from the vessel into the surrounding tissues.

Thrombosis: Occlusion of the lumen of the vascular access due to clots leading to low blood flow. This is confirmed by angiography or surgery.

Stenosis: Narrowing of the vessel lumen confirmed by vascular imaging such as duplex ultrasound.

Aneurysm: Progressive enlargement and weakening of the fistula wall which may lead to bleeding.

Abdominal pain: Pain occurring in the portion of the trunk of the body lying between the thorax and the pelvis. The pain can be any unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in only the perception of an uncomfortable stimulus but also the response to that perception.

Fluid Overload: Excess intravascular, interstitial and/or intracellular body fluids. This may manifest with swelling of the extremities, engorged neck vein and rales.

Hematuria: Blood in the urine.

Bleeding: Emitting blood, as from an injured vessel, body orifice, or mucosa.

Electrolyte imbalance involves the following based on serum levels. The definitions are from the CHL.

Hyponatremia: Sodium levels <130 mEq/L

Hypernatremia: Sodium levels >146 mEq/L

Hypokalemia: Potassium levels <3.0 mEq/L

Hyperkalemia: Potassium levels >5.6 mEq/L

Hypocalcemia: Calcium levels <8.0 mg/dL

Hypercalcemia: Calcium levels >10.5 mg/dL

Metabolic alkalosis: Bicarbonate level >29 mEq/L

Metabolic acidosis: Bicarbonate level <20 mEq/L

Hyperphosphatemia: Phosphorus levels >5.5 mg/dL

Hypophosphatemia: Phosphorus levels <2.2 mg/dL

Appendix 2: Elements of Informed Consent

Each human subject, or where the subject lacks legal capacity, the subject's legal representative, is to be informed by the Investigator that the IP being used is for investigational purposes. Pertinent information concerning the IP should be provided to enable the subject to make a decision as to his willingness to participate in the investigations. Informed consent is generally evidenced by a written agreement signed by the subject or his/her legal representative; such agreement shall include no language through which the subject waives, or appears to waive, any of the subject's legal rights or releases or appears to release the institution, the Sponsor, the Sponsor Partner, or the Investigator, from liability for negligence.

Both the informed consent discussion and the written informed consent form should include clear explanations of the following:

1. The trial involves research.

2. The purpose of the trial.

3. The trial treatment(s).

4. The trial procedures to be followed, including all invasive procedures.

5. The subject's responsibilities.

6. Those aspects of the trial that are experimental or exploratory.

7. The reasonably foreseeable risks or inconveniences to the subject, and when applicable, to an embryo, fetus, or nursing infant.

8. The reasonably expected benefits. Where there is no intended clinical benefit to the subject, the subject should be made aware of this.

9. The alternative procedure(s) or course(s) of treatment that may be available to the subject and their important potential benefits and risks.

10. The compensation and/or treatment available to the subject in the event of trial related injury.

11. The anticipated prorated payment, if any, to the subject for participating in the trial.

12. The anticipated expenses, if any, to the subject for participating in the trial.

13. That the subject's participation in the trial is voluntary and the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

14. That the monitor(s), auditor(s), the EC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

15. The records identifying the subject will be kept confidential and to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

16. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

17. The person(s) to contact for further information regarding the trial and the rights of trial subjects and whom to contact in the event of trial related injury.

18. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated without the subject's consent.

19. The expected duration of the subject's participation in the trial.

20. The approximate number of subjects involved in the trial.

21. The listing of the trial on ClinicalTrials.gov.

After the subject has read the form, the subject indicates understanding of it and consents to participate by signing and dating the form. The form should then be signed and dated by the person obtaining the Informed Consent.

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