CLINICAL TRIAL PROTOCOL

AN OPEN LABEL STUDY TO ALLOW PATIENTS CONTINUOUS USE OF THE HEMOCARE™ HEMODIALYSIS SYSTEM FOR HOME HEMODIALYSIS PRIOR TO MARKET AUTHORIZATION

Protocol Number: DKPL-00674-001

[redacted]

Sponsor: DEKA Research & Development

[redacted]

Version Number: 1.2 22 Jan 2022

[redacted]

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LIST OF ABBREVIATIONS

ADE	Adverse Device Effects
ADR	Adverse Drug Reactions
AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
aPTT	Activated Partial Thromboplastin Time
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase (SGOT)
AV	Arteriovenous
β-hCG	Serum Beta Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
CAPD	Continuous Ambulatory Peritoneal Dialysis
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HD	Hemodialysis
HIPAA	Health Information Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Standards Organization
ITT	Intent-To-Treat

[redacted]

Kt/V_{urea}	Dimensionless number used to quantify hemodialysis adequacy
MedDRA	Medical Dictionary for Regulatory Activities
OOS	Out-Of-Specification
PD	Peritoneal Dialysis
PI	Principal Investigator
PROs	Patient reported outcomes
PT	Preferred Term
RBC	Red Blood Cell (count)
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SAER	Serious Adverse Event Report
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
SOC	System Organ Class
$stdKt/V_{urea}$	Standard Kt/V_{urea} (see Kt/V_{urea})
SUSAR	Suspected unexpected serious adverse reactions
UADE	Unanticipated Adverse Device Effect
UF	Ultrafiltration
URR	Urea Reduction Ratio
US	United States
UV	Ultraviolet

Investigator Protocol Signature Page

Study Title: An Open Label Study to Allow Patients Continuous Use of the HemoCare™ Hemodialysis System for Home Hemodialysis Prior to Market Authorization

Protocol Number: DKPL-00674-001 v1.2

Final Date: 22 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. 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 treat with this device 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 outlined 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 SYNOPSIS

Protocol #:	DKPL-00674-001
Study Title:	An Open Label Study to Allow Patients Continuous Use of the HemoCare™ Hemodialysis System for Home Hemodialysis Prior to Market Authorization
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
Study Rationale:	To allow subjects who complete DEKA Protocol DKPL-00057-001 to continue to use the HemoCare™ Hemodialysis System during the completion of the study and during the review of the pre-market notifications for the devices in the HemoCare™ Hemodialysis System.
Study Objectives:	This rollover study is designed to monitor and access the safety of continued access to the HemoCare™ Hemodialysis System used during the completion of the DEKA Protocol DKPL-00057-001 study and during the review of the pre-market notifications for the devices in the HemoCare™ Hemodialysis System.
Endpoints:	**Safety Endpoint(s):** Safety will be assessed by evaluating adverse events and monthly laboratory draws [e.g., hemoglobin, BUN, creatinine, electrolytes, calcium, and phosphorus]. Adverse events will be mapped to a primary MedDRA SOC and PT. Anticipated AEs and SAEs (includes all adverse events related to dialysis as identified in Section 8.1.7) and unanticipated AEs and SAEs (excludes all adverse events related to dialysis identified in Section 8.1.7) will be summarized by SOC and PT. In addition, all device-related AEs and SAEs will be summarized by SOC and PT. An overview of the total number of AEs and SAEs (anticipated, unanticipated, and device-related) will be provided. In addition,

	an overview will be provided of the total number of subjects having at least one: a. anticipated AE b. anticipated SAE c. unanticipated AE d. unanticipated SAE e. device-related AE f. device-related SAE (UADE) The proportion of subjects having at least one AE within each of these six AE subgroups will be summarized descriptively. Furthermore, the proportion of subjects having AEs within each of these 6 AE subgroups will be summarized by SOC, PT and severity (mild, moderate or severe) for the most severe rating of each AE per subject. And, the AE rate per 100 HemoCare™ Hemodialysis System treatments will be calculated. Descriptive summary statistics will be provided for the visit values and change from baseline in monthly laboratory assessments. Baseline observation data for all assessments are defined in section 11.4 and unless otherwise specified therein, are the last observational values brought forward from DEKA Protocol DKPL-00057-001.
Study Population:	All subjects who complete DEKA Protocol DKPL-00057-001 and meet all of the inclusion criteria and exclusion criteria will be eligible to enroll into this extension study.
Study Duration:	Unless subject participation is discontinued prior to market authorization (e.g., subject withdrawal, investigator decision, Sponsor decision), enrolled subjects may continue treatment in this protocol until the HemoCare™ Hemodialysis System obtains market authorization.
Study Design and Methodology:	This is an open-label rollover study for subjects and care partners who have completed DEKA Protocol DKPL-00057-001. Enrolled subjects will continue to receive home hemodialysis per clinician prescription. Subjects will be seen in the clinic for monthly labs which, at a minimum, would include: hemoglobin, BUN, creatinine, electrolytes, calcium, and phosphorus. Water sampling will be done annually or as required by site policy or local regulations, ultrapure (water or dialysate) sampling will be done quarterly or as required by site policy or local regulations, and venous line infusion quality dialysate sampling will be done monthly.

Inclusion Criteria:	All of the following criteria must be met for the subject to be eligible for participation. This study will enroll subjects who: 1. Completed DEKA Protocol DKPL-00057-001 and are qualified to enter the study based on the assessment of the Investigator. 2. Are willing to comply and capable of complying with the study requirements for therapy with the HemoCare™ Hemodialysis System. 3. Have a trained study care partner able to support subject for all at-home study treatments. 4. Subject and care partner can read and understand English and provide written informed consent. 5. Have a stable functioning vascular access as judged by the treating physician.
Exclusion Criteria:	If anyof the following criteria are met, the potential subject will not be considered eligible for participation. This study will exclude subjects who: 1. Have a current self-reported pregnancy or are actively planning to become pregnant within the next 12 months, lactating, or not using medically acceptable means of contraception during the study. 2. Have any other clinically significant medical disease or condition or subject responsibility that, in the Investigator's opinion, may interfere with a subject's (and/or care partner's) ability to give informed consent, adhere to the protocol, interfere with assessment of the investigational product (IP), or serve as a contraindication to the subject's participation in the study. 3. 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. 4. Are participating or planning to participate in any other interventional studies except DKPL-00057-001.

[redacted]

Statistical Considerations:	**General Considerations:** Unless otherwise noted, all analyses will be performed using Statistical Analysis Software (SAS®), Version 9.4 SAS Institute Inc. **Determination of Sample Size:** Plan to enroll all subjects who complete DKPL-00057-001. The sample size is not based on a statistical power calculation. **Analysis Populations** The Intent-to-Treat (ITT) population will include all subjects who have used the HemoCare™ Hemodialysis System at least once in this rollover study. All analyses will be performed on the ITT population unless otherwise noted. **Study Endpoints:** **Safety Endpoint(s):** Safety will be assessed by evaluating adverse events and monthly laboratory draws [e.g., hemoglobin, BUN, creatinine, electrolytes, calcium, and phosphorus]. Adverse events will be mapped to a primary MedDRA SOC and PT. Anticipated AEs and SAEs (includes all adverse events related to dialysis as identified in Section 8.1.7) and unanticipated AEs and SAEs (excludes all adverse events related to dialysis identified in Section 8.1.7) will be summarized by SOC and PT. In addition, all device-related AEs and SAEs will be summarized by SOC and PT. An overview of the total number of AEs and SAEs (anticipated, unanticipated, and device-related) will be provided. In addition, an overview will be provided of the total number of subjects having at least one: a. anticipated AE b. anticipated SAE c. unanticipated AE d. unanticipated SAE e. device-related AE f. device-related SAE (UADE)

[redacted]

	The proportion of subjects having at least one AE within each of these six AE subgroups will be summarized descriptively. 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) for the most severe rating of each AE per subject. And, the AE rate per 100 HemoCare™ Hemodialysis System treatments will be calculated. Descriptive summary statistics will be provided for the visit values and change from baseline in monthly laboratory assessments. Baseline observation data for all assessments unless otherwise specified are the last observational values brought forward from DEKA Protocol DKPL-00057-001.

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 treatment in a dialysis center. 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 three 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 three to six 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 the safety of a home-based HD system used for hemodialysis in nocturnal home settings.

[redacted]

DEKA Protocol DKPL-00057-001 (Clinical Evaluation of The HemoCare™ Hemodialysis System for Home Nocturnal Hemodialysis) is currently enrolling up to 70 subjects who are receiving a regimen of HD at least 3 times every seven days in order to achieve approximately 30 subjects entering the Unassisted Home Evaluable Period. Eligible subjects and their care partners enter an In-Facility Introduction Period where training is conducted. Upon completion of training, subjects and their care partner enter a transition period (Transition Period A), followed by the Assisted Evaluable Period. During the Assisted Evaluable Period, subjects receive extended duration HD treatments (5-10 hours per treatment) administered by a Medical Professional prescribed to occur every other day, preferably in a home setting. After successful completion of the Assisted Evaluable Period, subjects enter a second transition period (Transition Period B) in the home setting. This will be followed by the Unassisted Home Evaluable Period where the subject and/or care partner will perform each treatment in the subject's home. Subjects will receive a minimum of 34 HD treatments (5-10 hours per treatment) in each Evaluable Period with treatments prescribed to occur every other day.

3 STUDY OBJECTIVE

This rollover study is designed to monitor and access the safety of continued access to the HemoCare™ Hemodialysis System used during the completion of the DEKA Protocol DKPL-00057-001 study and during the review of the pre-market notifications for the devices in the HemoCare™ Hemodialysis System.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is an open-label rollover study for subjects and care partners who have completed DEKA Protocol DKPL-00057-001. Enrolled subjects will receive home HD per clinician prescription. Subjects will be seen in the clinic for monthly labs which, at a minimum, would include: hemoglobin, BUN, creatinine, electrolytes, calcium, and phosphorus. Water sampling (AAMI Analysis) will be done once per year or as required by site policy or local regulations, ultrapure (water or dialysate) sampling will be quarterly or as required by site policy or local regulations, and venous line infusion quality dialysate sampling will be done monthly.

See Appendix 1, Study Events Table.

4.2 Rationale for Study Design and Control Group

To allow subjects who complete DEKA Protocol DKPL-00057-001 to continue using the HemoCare™ Hemodialysis System prior to market authorization.

4.3 Study Duration and Dates

The study will begin approximately 6 months after enrollment of the first subject in DEKA Protocol DKPL-00057-001 and end when the HemoCare™ Hemodialysis System receives market authorization.

5 STUDY POPULATION SELECTION

5.1 Study Population

All subjects from DEKA Protocol DKPL-00057-001 who meet all of the inclusion and none of the exclusion criteria will be eligible to enroll into this rollover study.

5.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

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

1. Completed DKPL-00057-001 and are qualified to enter the study based on the assessment of the Investigator.
2. Are willing to comply and capable of complying with the study requirements for therapy with the HemoCare™ Hemodialysis System.
3. Have a trained study care partner able to support subject for all at-home study treatments.
4. Can read and understand English and provide written informed consent (both the subject and care partner).
5. Have a stable functioning vascular access as judged by the treating physician.

5.3 Exclusion Criteria

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

1. Have a current self-reported pregnancy or are actively planning to become pregnant within the next 12 months, lactating, or not using medically acceptable means of contraception during the study.
2. Have any other clinically significant medical disease or condition or subject responsibility that, in the Investigator's opinion, may interfere with a subject's (and/or care partner's) ability to give informed consent, adhere to the protocol, interfere with assessment of the investigational product (IP), or serve as a contraindication to the subject's participation in the study.
3. 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.
4. Are participating or planning to participate in any other interventional studies except DKPL-00057-001.

5.4 Subject Discontinuation/Withdrawal

Subjects may be withdrawn/prematurely discontinued from the study for any of the following reasons:

1. Adverse event
2. Inadequate dialysis
3. Protocol violation (i.e., the subject failed to meet protocol entry criteria or did not adhere to the protocol requirements)
4. Pregnancy
5. Lost to follow-up (i.e., subject fails to return for study visits)
6. Voluntary withdrawal (i.e., subject's request)
7. Investigator's discretion
8. Renal transplantation
9. Switch to peritoneal dialysis (PD)
10. Subject death
11. Termination of study DKPL-00057-001 or DKPL-00674 -001
12. Marketing application withdrawal
13. Regulatory clearance/approval is not considered feasible
14. 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 the Investigator 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 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. The Investigator or designee should promptly inform their site monitor when any subject is discontinued from the study.

6 STUDY TREATMENT(S)

6.1 Enrollment, Randomization, and Assignment to a Treatment Group

All subjects who sign the informed consent form (ICF) (see Section 12.4) will continue to be assigned the same subject number as in DKPL-00057-001. Subjects confirmed to meet all of the inclusion criteria and none of the exclusion criteria will be considered enrolled.

Subjects will not be randomized. All enrolled subjects will continue treatment with the HemoCare™ Hemodialysis System.

6.2 Treatments Administered

Enrolled subjects will receive HemoCare™ Hemodialysis System treatments per clinician's prescription. An existing functioning vascular access will be used for dialysis. Treatments will be administered by trained subject and care partner.

6.3 Timing and Selection of Prescription Regimen for Each Subject

Treatment duration for each individual subject will vary based on the assigned prescription. Subjects will have the flexibility to alter the treatment parameters (e.g., frequency, duration, blood flow rate, etc.) on a treatment-by-treatment basis, within a range approved by the investigator. The subject's initial prescription and all treatment-by-treatment alterations will be transmitted to the study site and study database via the HemoCare™ Connectivity Platform, a cloud-based clinical software platform.

6.4 Blinding

This is an open-label study that will not require blinding of the IPs.

6.5 Concomitant Therapy

The Investigator should review any additions or changes in concomitant therapy. All medications should be recorded in the source documents or equivalent. Any new concomitant medications since the end of DEKA Protocol DKPL-00057-001, including dose, frequency, start and 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 by the HemoCare™ Hemodialysis System.

6.6 Excluded Concomitant Medications

No specific concomitant medication is restricted. No intravenous medications (other than heparin through the heparin pump) may be administered once the subject connects to the device or during treatment. All intravenous medications required for the subject must be administered either prior to connection or post-treatment directly through the access needle.

6.7 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.

6.8 Treatment Compliance

The subject/care partner will input required data into the HemoCare™ Hemodialysis System before and after each treatment.

The subject will be required to complete a Treatment Flowsheet at every treatment. Study subjects should be compliant with treatment, prescribed by their physician.

The site staff will complete a product accountability log to document all IP movement (receipt, dispense, return, and disposition). See Sections 6.10.2 for additional details.

6.9 Missed Treatments

Missed treatments will not be replaced unless judged by the Investigator as clinically indicated.

6.10 Description of Investigational Devices and Components

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]

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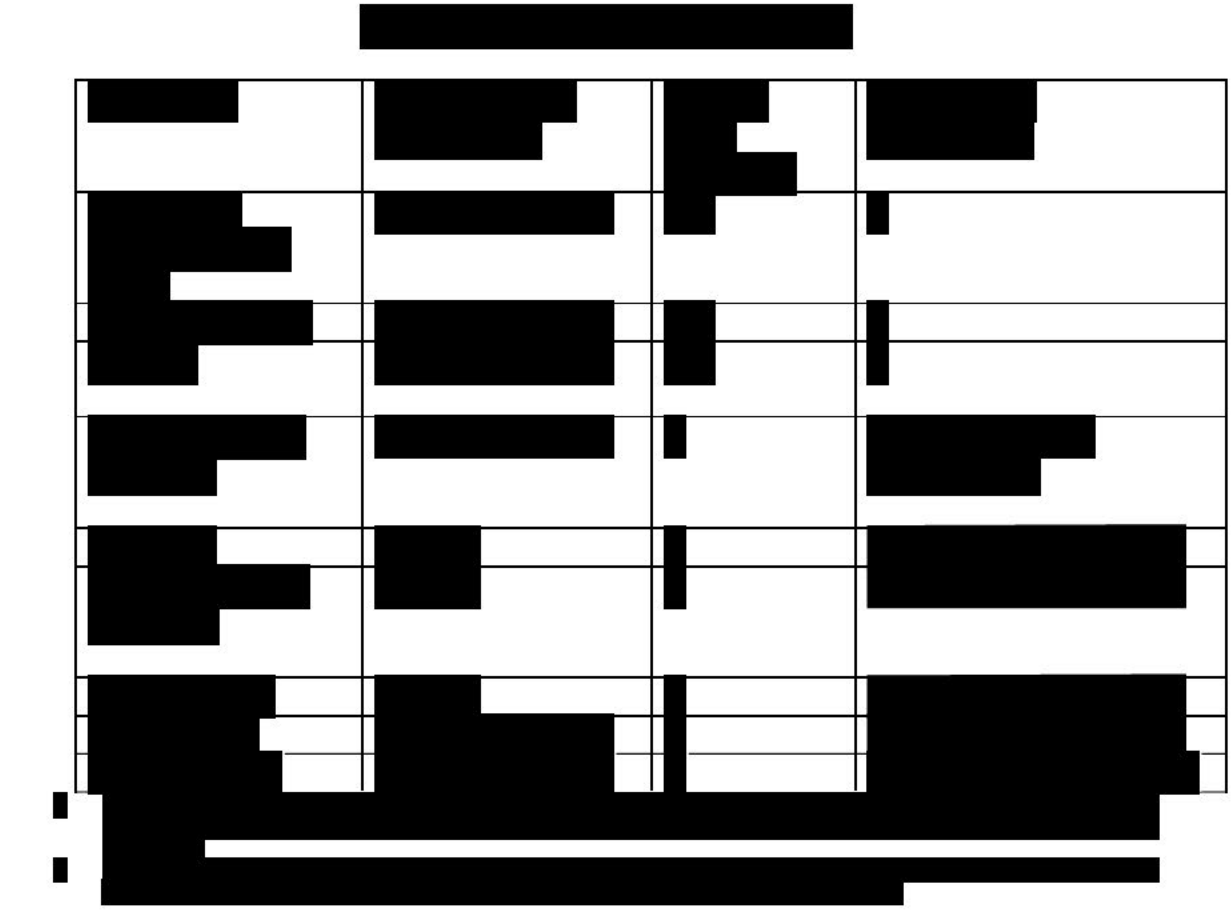

[redacted]

6.10.3 Accessibility and Control of Study Participant Data

In order to ship IP and 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 [redacted] 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]

7 STUDY ACTIVITIES

7.1 Demographics and Baseline Characteristics

Medical history and medications will be reviewed and updated as necessary. Demographics (age, gender, race, and ethnicity) were recorded in DEKA Protocol DKPL-00057-001. For this study, baseline observation data for all assessments are defined in section 11.4 and unless otherwise specified therein, are the last observational values brought forward from DEKA Protocol DKPL-00057-001.Physical Examination

Physical examinations will be performed at End of Study visit.

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

[redacted]

7.2 Vital Signs

Vital signs will include measurements of sitting blood pressure, sitting respiratory rate, temperature, and sitting pulse rate. Vital signs will be collected during treatment times and are explained in Section 7.7on Clinical Observations.

7.3 Kt/V

Weekly stdKt/V_{urea} will be calculated from pre- and post-dialysis urea levels. Blood samples will be obtained once a month mid-week. A central laboratory will be used for the analysis of the blood samples. If the weekly stdKt/V_{urea} goal ($\geq$ 2.0) is not met, the reason will be recorded.

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

7.4 Training on the HemoCare™ Hemodialysis System and Study Procedures

7.4.1 Study Site Team Training

HemoCare™ Hemodialysis System training tools developed specifically for use with the system will be utilized. All assigned new site team members will 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 refresher training (if Investigator deems necessary) on an as-needed basis by approved site training nurses. If a new care partner requires training, training will be provided by approved site training nurses.

[redacted]

[redacted]

7.7 Clinical Observations

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

- 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
- Pulse: both pre-dialysis and post-dialysis seated
- Body temperature: pre- and post-dialysis

A study nurse or their designee will collect study data monthly (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 7.8). The assessment may include blood pressure, fluid status, and dialysis prescription.

[redacted]

7.8 Treatment Flowsheet and Weekly Assessment

At every treatment with the HemoCare™ Hemodialysis System, subjects will complete a 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
- 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

[redacted] 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. Based on all data collected from the subject, the site staff will complete their source logs and eCRFs as appropriate. [redacted]

7.9 Water and Dialysate Sampling Analysis

Tap (feed) water used to feed the HemoCare™ Water Device shall meet EPA standards for drinking water. Product water shall not exceed 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

[redacted]

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 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.

7.9.1 Chemical Contaminants –Tap Water

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. Trial subjects can continue treating on HemoCare™ Hemodialysis Systems in these locations while the results are being analyzed.

7.9.2 Microbiological Cultures and Endotoxin – Ultrapure [redacted]

Ultrapure, [redacted] samples from HemoCare™ Hemodialysis System [redacted] will be collected from the device by Sponsor personnel or designees at least quarterly or according to local procedures after subject rolls over from DEKA Protocol DKPL-00057-001 study. If a new, not previously qualified, HemoCare™ Hemodialysis System is installed in the subject's home, the subject cannot be treated with the HemoCare™ Hemodialysis System until the results are received and reviewed by the trial site and Sponsor per the device User Guide. 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 [redacted] produced by the HemoCare™ Hemodialysis

[redacted]

System shall not exceed microbial or endotoxin levels as stated in 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.

7.9.3 Process for Responding to Out-of-Specification Results

7.9.3.1 Decision Tree

Clinical study decision trees for ultrapure samples have been developed and will be provided to study sites. These decision trees provide guidance to the clinical site and the DEKA R&D [redacted] team on appropriate actions to be taken in situations where 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 [redacted] if applicable. [redacted]

Additional actions are described as follows:

- Resample.
- All device logs evaluated for anomalies.
- Procedure checklists recorded during sample collection and processing reviewed for anomalies.
- Contract Laboratory will conduct an independent 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.

7.9.4 Chloramine, pH, and Conductivity Testing

Chloramine testing of the water for dialysis will be completed according to standard-of- care and local requirements.

[redacted]

[redacted]

8 ADVERSE EVENT REPORTING

8.1 Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a subject administered 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 (see Appendix 4).

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 the subject signs the ICF until the end of 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.

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

[redacted]

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 30 days post study completion. 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 the Sponsor 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) must 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 of the AE began.

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

Mild – Asymptomatic. 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.

[redacted]

Moderate – Produces limited impairment of daily function and can require minimal, local or non-invasive therapeutic intervention, but produces no sequelae.

Severe or Medically Significant – Requires hospitalization or prolonged hospitalization. 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 bythe 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 "probably associated," "possibly associated," "unlikely associated" and "not associated."

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.

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 Event

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 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 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 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;

[redacted]

abdominal pain; fluid overload; hematuria; bleeding; and electrolyte imbalance.[15-18] Definitions of these adverse reactions are providedin Appendix 4.

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.

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.

8.1.9 Performing Adverse Events Assessments

The AE collection period for each subject starts with the signing of the ICF 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 review of the treatment details in the HemoCare™ cloud-based system 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 solicitation, 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 solicit 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 gather AE information during the Weekly Assessment. The site team members will use their clinical judgment to follow up with the subjects and report any applicable event(s).

The site investigator or designee will contact the subject weekly to discuss their current status, treatment, and condition. These timelines are minimum requirements

for the sites to follow, and sites 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).

8.1.10 Adverse Event Reporting

8.1.10.1 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)
- Severity of the event (mild, moderate, or severe)
- Causality of the event (related to treatment and/or related to the IP)
- 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.

8.1.11 Expedited Reporting of Serious Adverse Events and Suspected Unexpected Serious Adverse Reaction (SUSAR)

The 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.

8.1.12 Device-Related Product Complaints

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

8.1.13 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 they occur [redacted]. 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 todevice reported product issues, trial sites will also report product issues.

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 Guide or training tools. The

site staff will assist the subject in resolving the product issue using the device User Guide and training material. If the site is unable to resolve the product issue, site staff 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]

8.2 Clinical Laboratory Tests

8.2.1 Laboratory Parameters

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

Sites may order additional activated partial thromboplastin time (aPTT) testing as necessary at the discretion of the Investigator in order to maintain optimal heparin dosing.

Subjects will be in a seated or supine position during blood collection. Clinical laboratory tests are found in Table 2.

Table 2. 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 phosphorus (pre-dialysis) • Urea (pre and post-dialysis) • Iron profile (pre-dialysis)	**Hematology:** • CBC (pre-dialysis) **Coagulation:** • Activated partial thromboplastin time (aPTT)

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

Laboratory evaluations will be performed as outlined in Appendix 2.

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 baseline 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.

Baseline observation data for all assessments are defined in section 11.4 and unless otherwise specified therein, are the last observational values brought forward from DEKA Protocol DKPL-00057-001, 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.

9 STUDY SCHEDULE AND PROCEDURES

9.1 Schedule of Evaluations and Procedures

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

9.2 Qualification Visit

The Qualification visit will be conducted after completion of DEKA Protocol DKPL-00057-001. The study must be explained to the subjects and care partners at this visit or prior, and all subjects and care partners 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 Qualification visit:

- Obtain informed consent of the subject and care partner.
- Update medical history including resolved AEs.
- Update concomitant medications.
- Update AEs including ongoing AEs.

9.3 Treatment Period

This period begins immediately following enrollment and will last until subject is discontinued from the study or Market Authorization for the HemoCare™ Hemodialysis System is granted. The following information will be collected, and procedures or evaluations will be performed:

- Treatment with the HemoCare™ Hemodialysis System as prescribed by the Investigator or designee. [redacted]
- Clinical laboratory evaluations as specified in Appendix 2.
- Care partner will be present for all treatments.
- At each treatment:
  - Clinical observations

[redacted]

- Adverse events/serious adverse events/adverse device effects
- Concomitant medications
- Treatment data from HemoCare™ Treatment Device
- [redacted]
- Device-related product issues (Device-related product complaints)
- Chloramine, and if applicable, pH and conductivity testing

- Ultrapure [redacted] sampling will be done quarterly or per site policy or local regulations. [redacted]
- The investigator or designee will assess each subject on a weekly basis according to standard-of-care and/or site regulations. The assessment may include blood pressure, fluid status and dialysis prescription.

9.4 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:

- 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 Appendix 2
- Device-related product issues (device-related product complaints)
- Device related AEs and SAEs will be followed post-study until resolution or stabilization

If a subject discontinues from the study, 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 as prescribed by their physician. The HemoCare Hemodialysis System used for these subjects will be removed from their home by the designee of the study sponsor.

[redacted]

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.

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

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 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 STATISTICAL CONSIDERATIONS

11.1 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.

Unless otherwise noted, all analyses will be performed using Statistical Analysis Software (SAS®), SAS/GRAPH® and SAS/STAT® software, Version 9.4 of SAS for Windows, copyright© 2002-2008 SAS Institute Inc., on a Microsoft Windows Server. Statistical Analysis Software and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA).[19]

11.2 Determination of Sample Size

Plan to enroll all subjects who complete the DEKA Protocol DKPL-00057-001. The sample size is not based on a statistical power calculation.

11.3 Analysis Populations

The Intent-to-Treat (ITT) population will include all subjects who have used the HemoCare™ Hemodialysis System at least once in this rollover study. All analyses will be performed on the ITT population unless otherwise noted.

11.4 Demographics and Baseline Characteristics

Demographic data include age, gender, race, body mass index (calculated as weight/height×height [kg/m^2]), and ethnicity.

Baseline observation data for all assessments are defined herein and unless otherwise specified, are the last observational values brought forward from DEKA Protocol DKPL-00057-001.

Other baseline data include:

1. General medical history; medical condition or surgery items collected on the eCRF will be coded to the appropriate System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.1 or higher.
2. Renal medical history,

[redacted]

a. type of first chronic dialysis treatment (HD or PD)
b. primary renal disease etiology
c. elapsed time since first chronic dialysis treatment of HD or PD and by modality (years)

3. Vital signs including height (cm), weight (kg), blood pressures (mmHg), pulse rate (beat/minute), temperature (degrees C), and respiratory rate (breaths/minute)
4. Hemodialysis prescription parameters from End of Study visit of DEKA Protocol DKPL-00057-001.
    a. duration of treatment session (hours)
    b. calculated total treatment time per week across all sessions (hours)
    c. blood flow rate (mL/minute)
    d. dialysate flow rate (mL/minute)
    e. dialysate volume (L)
    f. heparin loading dose (units)
    g. total heparin infusion (units)
    h. target dry weight (kg)
    i. total fluid removed (L) and weight loss (kg)
5. Type and location of dialysis access
6. Laboratory parameters from End of Study visit of DEKA Protocol DKPL-00057-001.
    a. CBC
    b. Comprehensive metabolic panel plus serum phosphorus
    c. Iron profile

Continuous variables will be summarized by sample size (N), mean, standard deviation, minimum, and maximum. Frequency and percentages will be provided for the categorical variables.

11.5 Primary Endpoints

11.5.1 Primary Safety Endpoint(s)

Safety endpoints will summarize the number of subjects having AE and the number of AE: Number and proportion of subjects having AE and SAE, Number of AE and SAE, and rate of AE/100-Treatment and SAE/100-Treatment.

All the above indicator will be broken down by SOC, PT, Anticipated/unanticipated, and Related/un-related.

Safety will be assessed by evaluating AEs. In addition, monthly laboratory draws will be assessed.

Adverse events will be mapped to a primary MedDRA SOC and PT. Anticipated AEs and SAEs (includes all AEs related to dialysis as identified in Section 8.1.7) and unanticipated AEs and SAEs (excludes all AEs related to dialysis identified in Section 8.1.7) will be summarized during by SOC and PT. In addition, all device-related AEs and SAEs will be summarized by SOC and PT.

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

a. anticipated AE

b. anticipated SAE

c. unanticipated AE

d. unanticipated SAE

e. device-related AE

f. device-related SAE (UADE)

The proportion of subjects having at least one AE within each of these six AE subgroups will be summarized descriptively.

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) for the most severe rating of each AE per subject. And, the AE rate per 100 HemoCare™ Hemodialysis System treatments will be calculated.

Descriptive summary statistics will be provided for the visit values and change from DEKA Protocol DKPL-00057-001 baseline in monthly laboratory draws.

11.7 Interim Analysis

An interim analysis is not planned for this study.

12 ADMINISTRATIVE CONSIDERATIONS

12.1 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 ofthe 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 the 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 the 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.

12.2 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.[20]

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.

12.3 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 Pharmacy Inc., a CVS Health Company, in writing; agreed to by the Investigator in writing; and approved by the Investigator's IRB/REB in writing prior to implementation of the amendment.

12.4 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 PI 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 5 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 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.

12.5 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]

12.6 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.

12.7 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.

[redacted]

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 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 Sponsor/designee immediately.

12.8 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/designee, whichever is longer. The PI must contact the Sponsor before destroying any records associated with the study. 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). The Sponsor/designee will be notified in writing of any such transfer.

12.9 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.

13 REFERENCE LIST

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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 Schedule of Evaluations and Procedures

Schedule of Evaluations and Procedures

Observation	Qualification Visit	Each Visit During Treatment Period	End of Study Visit
Informed Consent of subject and care partner	X		
Medical History Update[1]	X		
Physical examination			X
Vital signs		X	
Weekly Assessment by the investigator or designee		X	
Clinical observations[2]		X	X
AE/SAE/ADE[3]	X	X	X
Concomitant medications update[4]	X	X	X
Clinical laboratory evaluations[5]		X	X
Machine observations[6]		X	
Ultrapure [redacted] sampling[7]		X	
Visual assessment of the HemoCare™ Blood Treatment Set[8]		X	
Device-related product issues (Device-related complaints)[9]		X	X
Chloramine, pH, and conductivity testing[10]		X	
[redacted]		[redacted]	

[redacted] Adverse events that have resolved as of DKPL-00057-001 end of study visit will be included as medical history.
2. Clinical observations will occur per treatment.
3. Ongoing AEs and SAEs will be included from DKPL-00057-001 and any new AEs and SAEs will be collected after the informed consent is signed. ADEs will be collected from the first connections of the subject to the HemoCare™ Hemodialysis System.
4. Ongoing medications and any new medications taken will be recorded throughout the study.
5. Clinical laboratory evaluations are presented in detail in Appendix 2.
6. [redacted]
7. Ultrapure samples will be collected at least quarterly or according site policy or to local regulations after subject rolls over from Protocol DKPL-00057-001.
8. Visual assessment of the HemoCare™ Blood Treatment Set will occur before every treatment on the HemoCare™ Hemodialysis System.
9. Collection of device-related product issues (device-related complaints) will begin at the time the HemoCare™ Hemodialysis System is installed at the investigational site and assigned to a subject and this will continue throughout the entire study.
10. Chloramine, pH, and conductivity testing will occur before every treatment on the HemoCare™ Hemodialysis System according to standard-of-care and localrequirements.
11. [redacted]

[redacted]

Appendix 2 Schedule of Clinical Laboratory Evaluations

Schedule of Clinical Laboratory Evaluations

Observation	Qualification Visit	Treatment Period	End of Study Visit
CBC (pre-dialysis)[1]		X	X
Iron profile (pre-dialysis)[2]		X	X
Comprehensive metabolic panel (CMP) + serum phosphorus (pre-dialysis)[3]		X	X
Urea (pre and post-dialysis) [4]		X	
Kt/V calculation (pre and post-urea)[4]		X	
aPTT[5]		X	

1. A pre-dialysis CBC will be done 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. CMP 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 monthly during the study.
4. Kt/V is derived from pre and post-dialysis serum urea levels. Blood samples will be obtained once a month mid-week for Kt/V to be calculated.
5. Sites may order additional activated partial thromboplastin time (aPTT) testing as necessary at the discretion of the Investigator in order to maintain optimal heparin dosing.

[redacted]

Appendix 3 Proposed Management of Low Serum Phosphorus

More frequent and prolonged hemodialysis (HD) may lead to lowering of the serum phosphorus level. The FHN Nocturnal study showed subjects treated with 6-8 hours dialysis 5 or 6 times per week had 1.24 mg/dL decrease in mean serum phosphorus in comparison to conventional 3 times weekly dialysis subjects.[22] In the Nocturnal subjects, 73% did not need phosphate binders at 12 months compared to conventional dialysis.[22] In the Alberta Study, serum phosphorus decreased an average of 0.49 mmol/L in the nocturnal HD subjects vs conventional HD subjects. The difference between the two groups was noted as early as 2 months, and 77% of the nocturnal subjects discontinued all phosphate binders.[23]

There are well-established clinical approaches to management of high serum phosphorus levels including more frequent and prolonged dialysis.[24-26] As lowering of serum phosphorus levels are encountered very often with frequent and prolonged dialysis, the following guideline was created to assist the clinicians in management of their subjects with low serum phosphorus.

Monitoring

Measure serum phosphorus during the study per the schedule detailed in the protocol. The results as available should be evaluated by the investigator or designee. The pre-dialysis target phosphorus level will be 2.7 mg/dL - 5.5 mg/dL (0.87 mmol/L - 1.77 mmol/L).[27]

Review of Results

The investigator or designee will review the result and address the low serum phosphorus immediately and document results with treatment plan.

Guideline

If there is a trend for decreasing serum phosphorus close to lower limit (2.7 mg/dL or 0.87 mmol/L) sequentially decrease or stop the phosphate binders. Consider dietary advice to increase phosphorus intake. Document the medication and dietary changes. Repeat serum phosphorus as indicated.

Guideline for phosphate binder adjustment:

To provide guidance on the use of oral phosphate binders, we used a model ofphosphorus kinetics to simulated subjects treated 4, 5 or 6 times per week for 8 hours at blood and dialysate flow rates of 300 mL/min with the number of oral phosphate binders assumed to achieve a median pre-dialysis serum phosphorus concentration for the 774 subjects from the HEMO Study of approximately 3.0 mg/dL.[28-30] The number of oral phosphate binders

was then varied to estimate the effect of a change in 2 effective phosphorus binder dose (EPBD) on the pre-dialysis serum phosphorus concentration.[22] The results for these simulations are tabulated below:

	Increase in Serum Phosphorus Concentration (in mg/dL) by Decreasing the EPBD by 2 g per day		
Treatments per week	Median	10th Percentile	90th Percentile
4	0.58	0.47	0.73
5	0.47	0.37	0.59
6	0.39	0.31	0.50

If serum phosphorus continues to decrease below 2.2 mg/dL (0.7 mmol/L) despite the discontinuation of phosphate binders and liberalization of phosphorus intake, consider adjusting the dialysis prescription.

Guideline for blood and dialysis flow rate adjustment:

To provide guidance on the effect of simultaneously lowering the blood and dialysate flow rates (Q_B and Qd, respectively) on the pre-dialysis serum phosphorus concentration, we performed additional simulations from the base conditions described above. Tabulated below are the results (median value [10th percentile - 90th percentile]) from those simulations:

	Increase in Serum Phosphorus Concentration (in mg/dL) by Decreasing Q_B from 300 mL/min		
Treatments per week	Q_B=250 mL/min	Q_B=200 mL/min	Q_B=150 mL/min
4	0.15 [0.11-0.21]	0.38 [0.27-0.54]	0.77 [0.54-1.08]
5	0.15 [0.11-0.19]	0.36 [0.27-0.49]	0.74 [0.55-0.99]
6	0.14 [0.11-0.18]	0.35 [0.28-0.46]	0.71 [0.56-0.92]

The effect of decreasing Q_B and Q_D on the serum phosphorus concentration is relatively consistent whether subjects are treated 4, 5 or 6 times per week. The effect of simultaneously altering the oral phosphate binder prescription and flow rates can be obtained by combining the results in the above tables (Phosphate binder and dialysate flow adjustments).

[redacted]

Appendix 4 Adverse Reactions Related to Hemodialysis Therapy

Hypotension: Decrease in systolic blood pressure of at least 20 mmHg or decrease in mean arterial pressure of 10 mmHg in combination with symptoms such as nausea, vomiting, muscle cramps, dizziness, fainting. The reference value is the subject's own blood pressure taken when subject is seated quietly in the chair for at least 5 minutes with feet on the floor and arm supported at heart level as described by Joint National Committee 7 recommendation.

Hypertension: Any increase in mean arterial pressure of 15 mmHg or more during or immediately after hemodialysis. The reference value is the subject's own blood pressure taken when subject is seated quietly in the chair for at least 5 minutes with feet on the floor and arm supported at heart level as described by Joint National Committee 7 recommendation.

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. The normal temperature taken orally ranges from 37°C to 39°C. Temperatures documented above 39°C would be considered an adverse event.

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 respiratorysupport 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 tachycardia, 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-tachysyndromes.

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), and 3. Dialysis solution contaminated with formaldehyde, bleach, chloramines (from city water supply), copper (from copper piping), fluoride, nitrates (from water supply), zinc, and 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 and an inadvertently opened end of a central venous catheter. Micro-air bubbles can become trapped in the hollow fibers of the dialyzer reducing efficiency of dialysis and can also lead to clotting of the circuit.

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.

[redacted]

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/dLHypercalcemia: Calcium levels >10.5
mg/dLMetabolic alkalosis: Bicarbonate level >29
mEq/L Metabolic acidosis: Bicarbonate level <20
mEq/L

Appendix 5 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 decide 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) and the probability for random assignment to each treatment.
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.

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 InformedConsent.

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.

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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