AN OPEN LABEL PHASE 1 STUDY TO COMPARE THE SAFETY AND TOLERABILITY OF THE [redacted] COLUMN AT DIFFERENT BLOOD-FLOW RATES IN PATIENTS WITH END-STAGE RENAL DISEASE UNDERGOING HEMODIALYSIS

Protocol Number:	AKST1210-101 NCT: NCT04985383
Clinical Phase:	1
Sponsor:	Alkahest, Inc. 125 Shoreway Road, Suite D San Carlos, CA 94070
Study Agent:	[redacted] β2 microglobulin (b2M) apheresis column (also known as AKST1210)
Indications:	End-stage renal disease with cognitive impairment [redacted] in patients on hemodialysis
Authorized Representative:	[redacted]
Version Number:	2.1
Version Date:	13MAY2021
Replaces Version(s):	2.0, 12APR2021

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACT	Activated clotting time
ACTH	Adrenocorticotropic hormone
ADE	Adverse device effect
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
b2M	Beta 2-microglobulin, β_2-microglobulin
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CH50	Total hemolytic complement
CK	Creatine kinase
CMP	Clinical Monitoring Plan
HCO_3	Bicarbonate
CRA	Clinical research associate
CRF	Case report form
CRO	Contract Research Organization
DBP	Diastolic blood pressure
[redacted]	[redacted]
ECG	Electrocardiogram
ENT	Ear, nose, throat
EOS	End of Study
EOT	End of Treatment
ESA	Erythropoiesis-stimulating agents
ESRD	End-stage renal disease
ESRD-CI	End-stage renal disease with cognitive impairment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCV Ab	Hepatitis C antibody
HD	Hemodialysis
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonisation

ICH E6 R2	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidance for Industry, Good Clinical Practice: Consolidated Guidance, Revision 2
IDE	Investigational Device Exemption
IDH	Intradialytic hypotension/hypotensive event
IGFBP1	Insulin-like growth factor protein 1
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
Kt/V	Fractional urea clearance
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
PRAE	Procedure-related adverse event
PT	Preferred Term; prothrombin time
PT/INR	Prothrombin time/international normalized ratio
PVG	Pharmacovigilance
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's correction formula
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical Analytical Plan
SBP	Systolic blood pressure
SC5b-9	Soluble membrane attack complex
SD	Standard deviation
SOC	System Organ Class
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event
TSH	Thyroid-stimulating hormone
UADE	Unanticipated adverse device effect
UFR	Ultrafiltration rate
URR	Urea reduction ratio
US	United States
WOCBP	Women of childbearing potential

LIST OF DEFINITIONS

Intradialytic hypotension/hypotensive event (IDH)	A systolic blood pressure (SBP) < 90 mmHg that occurs during hemodialysis and is confirmed by repeat measurement.
Expected IDH Rate	The expected number of occurrences of IDH per weekly treatment period derived from a subject's Historical IDH rate (see row below and also Appendix 17.1). The expected IDH Rate is compared with the actual IDH rate and used to assess escalation, de-escalation, and discontinuation.
Historical IDH Rate	The number of occurrences of IDH as documented in a subject's medical record during a recent 8-week period prior to the run-in period. Subjects with 7 or more IDH events during this 8-week interval will be excluded.

PROTOCOL APPROVAL PAGE

Study Title:	An Open Label Phase 1 Study to Compare the Safety and Tolerability of the [redacted] Column at Different Blood-Flow Rates in Patients with End-Stage Renal Disease Undergoing Hemodialysis
Protocol Number:	AKST1210-101
Version/Date:	V2.1, 13MAY2021
Sponsor Name and Address:	Alkahest, Inc. 125 Shoreway Road, Suite D San Carlos, CA 94070

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practice, the Declaration of Helsinki in the latest relevant version, and applicable legal and regulatory requirements.

Approved by:

STATEMENT OF COMPLIANCE

Protocol Title: An Open Label Phase 1 Study to Compare the Safety and Tolerablity of the [redacted] Column at Different Blood-Flow Rates in Patients with End-Stage Renal Disease Undergoing Hemodialysis

Protocol Number: AKST1210-101

Version/Date: V2.1, 13MAY2021

By my signature, I:

- Confirm that my staff and I have carefully read and understand this protocol or protocol amendment, have received the Investigator Brochure, and are thoroughly familiar with the appropriate use of the investigational agent described herein.
- Agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by the Sponsor, Alkahest, Inc., or their designee.
- Agree to assume responsibility for the proper conduct of the study at this site, including complying with current relevant versions of the United States (US) Food and Drug Administration (FDA) regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human subjects.
- Agree not to implement deviations from or changes to the protocol or protocol amendments without agreement from the Sponsor and prior submission to and written approval (where required) from the Institutional Review Board (IRB) except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Agree to onsite monitoring of all source documents by Alkahest, Inc. or designee and to onsite inspection of source documents by appropriate regulatory authorities, including but not limited to the FDA, local governing regulatory bodies, and IRB inspectors.

Investigator's Signature Date

Print Name

PROTOCOL SUMMARY

Title: An Open Label Phase 1 Study to Compare the Safety and Tolerablity of the [redacted] Column at Different Blood-Flow Rates in Patients with End-Stage Renal Disease Undergoing Hemodialysis

Objective: The objective of this study is to evaluate the safety and tolerability of the [redacted] column at blood-flow rates greater than 250 mL/min in subjects with end-stage renal disease (ESRD) undergoing hemodialysis (HD). The study will assess the safety, tolerability, and impact on HD parameters when the [redacted] column is used at a blood-flow of up to 450 mL/min.

Précis: This is an open-label study in 12 to 15 subjects between 40 and 75 years of age with ESRD on HD. The purpose of the study is to compare the safety and tolerability of two blood-flow rates when the b2M [redacted] column is used during HD. The [redacted] column was originally developed for blood-flow rates of 250 mL/min, and in this study it will be evaluated at both 250 mL/min and up to 450 mL/min.

After screening (Visit 1), subjects will undergo HD at a lower blood-flow rate (250 mL/min) for a 1-week run-in period to determine the HD duration required to achieve adequate fractional urea clearance (Kt/V) (> 1.2). Daugirdas' formula will be used to calculate Kt/V (Daugirdas 1993, Daugirdas 1995, Daugirdas and Schneditz 1995).

The [redacted] column comes in 3 sizes (S-15, S-25, S-35) and each size will be tested at blood-flow rates of 250 mL/min and up to 450 mL/min as tolerated (see Appendix 17.1: Escalation, De-escalation, and Discontinuation Rules for Treatment with the [redacted] Column). Each column-size and blood-flow rate combination will be evaluated during 3 consecutive HD sessions before proceeding with the next combination, as follows:

- Week -1 (Visits 2-4) HD run-in period (no column) at 250 mL/min to determine Kt/V
- Week 1 (Visits 5-7) [redacted] column S-15 at 250 mL/min
- Week 2 (Visits 8-10) [redacted] column S-15 at up to 450 mL/min
- Week 3 (Visits 11-13) [redacted] column S-25 at 250 mL/min
- Week 4 (Visits 14-16) [redacted] column S-25 at up to 450 mL/min
- Week 5 (Visits 17-19) [redacted] column S-35 at 250 mL/min
- Week 6 (Visits 20-22) [redacted] column S-35 at up to 450 mL/min
- Week 7 (Visit 23) End of study (EOS), no column, HD at patient's standard rate

The first treatment with the [redacted] column S-15 (150 mL) will occur mid-week (e.g., on Wednesday for subjects on a Monday/Wednesday/Friday schedule and on Thursday for subjects on a Tuesday/Thursday/Saturday schedule).

The escalation to the subsequent column-size and flow-rate combination will occur mid-week (e.g., on Wednesday for subjects on a Monday/Wednesday/Friday schedule and on Thursday for subjects on a Tuesday/Thursday/Saturday schedule).

The duration of each HD treatment will be adjusted to ensure adequate Kt/V with a reduced flow rate (approximately 4-6 hours at 250 mL/min, 3-4 hours at up to 450 mL/min). During each week determination of HD adequacy will include KtV > 1.2 (calculated from measurements of blood urea) and urea reduction ratio (URR) (weekly URR > 65%).

The most important known potential risk for use of the [redacted] column is an increased risk of IDH. Risk mitigations may include prophylactic administration of saline, supine positioning/lower limb elevation, avoidance of fasting before HD, avoidance of food intake during HD, use of cooled dialysate, education about the importance of avoiding excessive fluid gain between HD sessions (interdialytic weight gain), and avoiding the use of ultrafiltration rates (UFR) above 13 mL/kg/h. Concomitant medications, especially medications related to or affecting blood pressure (BP), should remain stable while on study and receiving HD with the [redacted] column.

The occurrence of IDH events during each week, as outlined in Appendix 17.1: Escalation, De-escalation, and Discontinuation Rules for Treatment with the [redacted] Column, will be one factor used to determine column size/blood-flow rate escalation/de-escalation as well as discontinuation from the study. There is also a possibility that the blood-flow rate of 450 mL/min cannot be attained due to factors related to the dialysis circuit or other technical issues. If the blood-flow rate of 450 mL/min cannot be attained, it can be adjusted down to enable continued dialysis at a blood-flow rate as high as possible. The reason(s) for the inability to attain a blood-flow rate of 450 mL/min must be documented.

Endpoints:

Primary Endpoints:

- Safety and tolerability of each column size at each blood-flow rate.
  - Evaluation of safety and tolerability will include assessment of the rate and severity of all adverse events (AEs), with analyses of adverse device effects (ADEs), treatment-emergent AEs (TEAEs), number of IDH events, and changes in total and free hemoglobin (Hgb).
  - Tolerability will be assessed by the proportion of subjects who can escalate to and tolerate each column size and blood-flow-rate combination.

Secondary Endpoints

- Weekly Kt/V and URR.
- Total fluid balance for each column-size flow-rate combination.
- Proportion of subjects who are able to achieve the dry weight goal during the allotted HD duration for each column size and flow rate combination.
- Change in plasma b2M concentrations (before and after HD) and contribution of the [redacted] column to b2M removal at each column size and blood-flow rate.
- Number of occurrences of visible thrombosis (clotting) in the [redacted] column, dialyzer, and/or tubing.
- Changes in plasma levels of complement factors, including total hemolytic complement (CH50), soluble membrane attack complex (SC5b-9), and C5a.
- Changes in plasma levels of other proteins, including insulin, adrenocorticotropic hormone (ACTH), insulin-like growth-factor protein 1 (IGFBP1), etc.

Population: Approximately 15 subjects between 40 and 75 years of age with ESRD will be enrolled. Assuming a drop-out rate of 20% (unrelated to safety) enrollment will yield approximately 12 evaluable subjects. Ultimately, the clinical conditions to be treated are patients with ESRD on maintenance HD who have a diagnosis of [redacted] ESRD with cognitive impairment (ESRD-CI).

Phase: 1

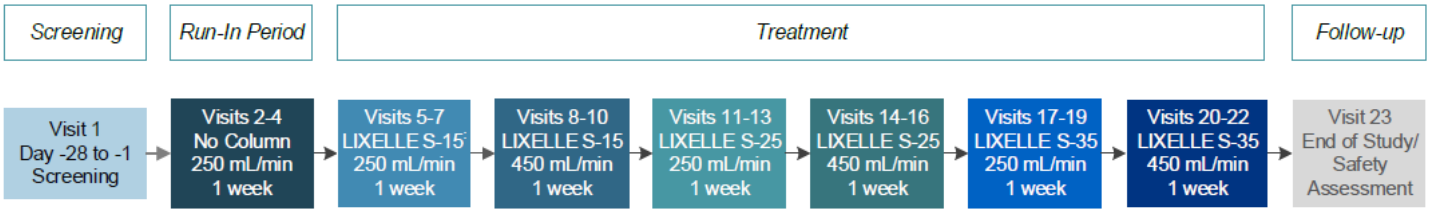
Number of Sites: Up to 4, US only

Description of Study Device: The [redacted] column (also known as AKST1210) is an adsorbent column containing porous, spherical cellulose beads with covalently linked hexadecyl groups as ligands. The [redacted] column adsorbs b2M by the combined use of hydrophobic interaction and the appropriate pore size on cellulose beads. The [redacted] column selectively binds b2M (11.8 kDa), with a positive correlation occurring between the amount of the b2M adsorbed and the pretreatment serum b2M concentration in both in vitro and clinical uses, while keeping essential proteins such as albumin remaining in blood circulation.

Study Duration: Approximately 7 months

Subject Participation: Approximately 12 weeks (up to 4 weeks for screening and 8 weeks on study, inclusive of the 1-week run-in period)

SCHEMATIC OF STUDY DESIGN



For information regarding rules for de-escalation and discontinuation see Appendix 17.1.

1. KEY ROLES

1.1. Authorized Representative (Signatory) / Responsible Party

1.2. Study Organization

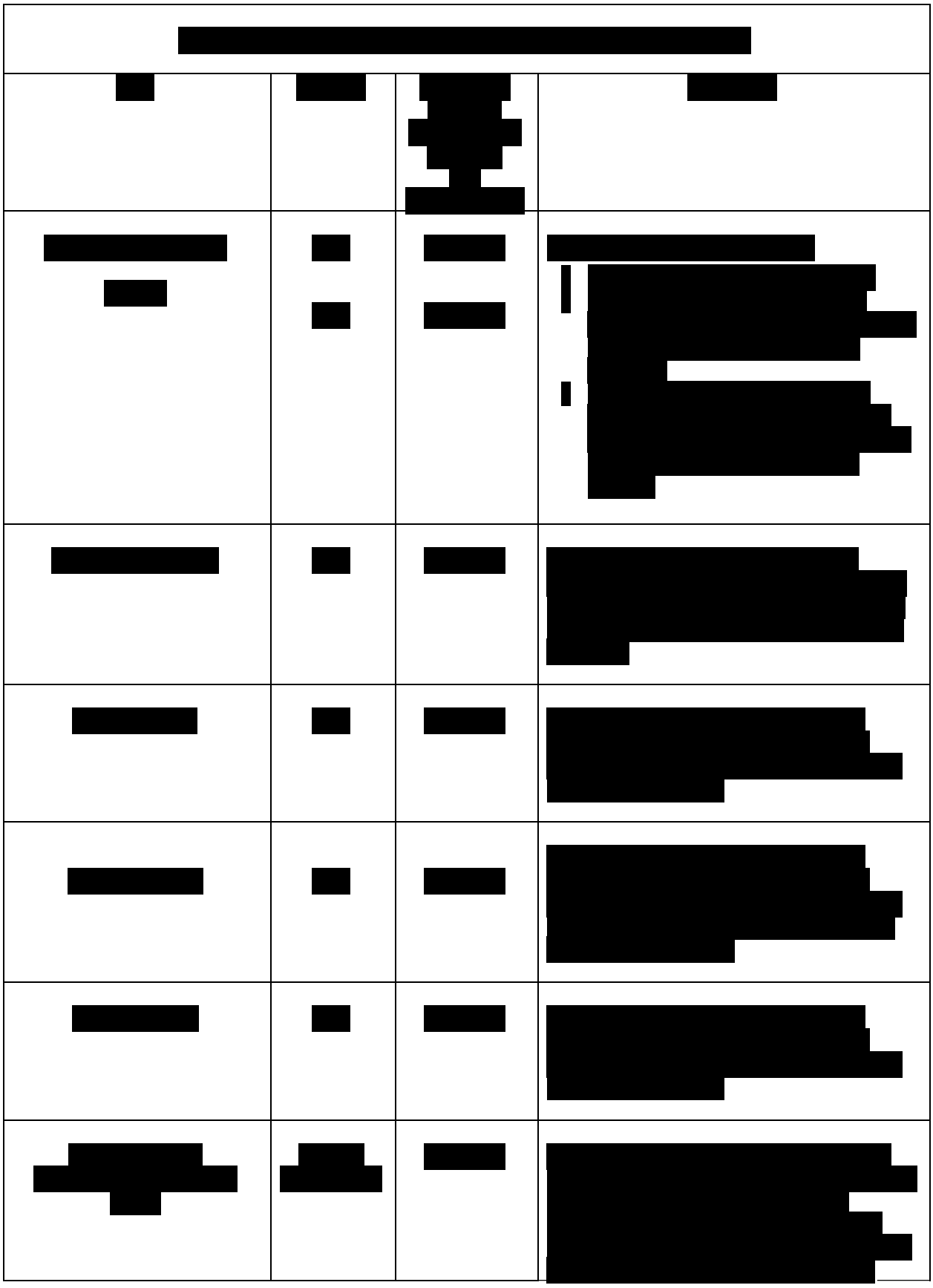
The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), Sponsor's medical expert and study monitor, Sponsor's representative(s), laboratories, steering committees, and oversight committees (including IRBs, as applicable) will be maintained by the Sponsor, or their designee, and provided to the investigator.

2. INTRODUCTION

[redacted]

2.2. Potential Risks and Benefits

[redacted]



3. OBJECTIVES AND PURPOSE

The objective of this study is to explore the safety and tolerability of the [redacted] column at blood-flow rates greater than 250 mL/min in subjects with ESRD undergoing HD. The proposed study will assess the safety, tolerability, and impact on HD parameters when the [redacted] column is used at a blood-flow rates of up to 450 mL/min. Secondary objectives include exploration of the performance of the column by measuring b2M concentrations before and after HD as well as the potential impact on other plasma proteins, including complement factors.

4. STUDY DESIGN AND ENDPOINTS

4.1. Description of the Study Design

This is an open-label study in subjects between 40 and 75 years of age who have ESRD requiring HD. Assuming a drop-out rate (unrelated to safety and tolerability) of 20%, approximately 15 subjects will be enrolled to obtain 12 evaluable subjects. The [redacted] column will be connected in series before (upstream) of the dialysis cartridge for the duration of each HD session. Only single-use dialyzers will be used during the study.

After screening (Visit 1), subjects will undergo HD at a lower blood-flow rate (250 mL/min) for a 1-week run-in period to determine the HD duration required to achieve adequate Kt/V (> 1.2). Daugirdas' formula will be used to calculate Kt/V (Daugirdas 1993, Daugirdas 1995, Daugirdas and Schneditz 1995).

The [redacted] column size will be increased from S-15 (150 mL) to S-25 (250 mL) to S-35 (350 mL), as tolerated, and blood-flow rates will be evaluated at 250 mL/min and up to 450 mL/min as tolerated (see Appendix 17.1: Escalation, De-escalation, and Discontinuation Rules for Treatment with the [redacted] Column). Each column-size and blood-flow rate combination will be evaluated during 3 consecutive HD sessions (1 week) before proceeding with the next combination, as follows (and as shown in the Schematic of Study Design):

- Week -1 (Visits 2-4) HD run-in period (no column) at 250 mL/min to determine Kt/V
- Week 1 (Visits 5-7) [redacted] column S-15 at 250 mL/min
- Week 2 (Visits 8-10) [redacted] column S-15 at up to 450 mL/min
- Week 3 (Visits 11-13) [redacted] column S-25 at 250 mL/min
- Week 4 (Visits 14-16) [redacted] column S-25 at up to 450 mL/min
- Week 5 (Visits 17-19) [redacted] column S-35 at 250 mL/min
- Week 6 (Visits 20-22) [redacted] column S-35 at up to 450 mL/min
- Week 7 (Visit 23) EOS, no column, HD at patient's standard rate

The first treatment with the [redacted] column S-15 (150 mL) will occur mid-week (e.g., on Wednesday for subjects on a Monday/Wednesday/Friday schedule and on Thursday for subjects on a Tuesday/Thursday/Saturday schedule).

The escalation to the subsequent column-size and flow-rate combination will occur mid-week (e.g., on Wednesday for subjects on a Monday/Wednesday/Friday schedule and on Thursday for subjects on a Tuesday/Thursday/Saturday schedule).

The duration of HD time will be adjusted for flow rate (approximately 4-6 hours for 250 mL/min, 3-4 hours for up to 450 mL/min). During each HD session, measurements of HD effectiveness will include Kt/V > 1.2 (calculated from measurements of blood urea) and URR (weekly URR > 65%).

The incidence of IDH events, as defined in Appendix 17.1: Escalation, De-escalation, and Discontinuation Rules for Treatment with the [redacted] Column, will be one factor used to determine column size/blood-flow rate escalation/de-escalation as well as discontinuation from the study.

The planned duration of subject participation is approximately 12 weeks (up to 4 weeks for screening and 8 weeks on-study, which is inclusive of the 1-week run-in period).

4.2. Study Endpoints

4.2.1. Primary Endpoints

- Safety and tolerability of each column size and each blood-flow rate.
    - Evaluation of safety and tolerability will include assessment of the rate and severity of all AEs, with analyses of ADEs, TEAEs, number of IDH events, and changes in total and free Hgb.
    - Tolerability will be assessed by the proportion of subjects who can escalate to and tolerate each column size and blood-flow-rate combination.

4.2.2. Secondary Endpoints

- Weekly Kt/V and URR.
- Total fluid balance for each column-size flow-rate combination.
- Proportion of subjects who are able to achieve the dry weight goal during the allotted HD duration for each column size and flow rate combination.
- Change in plasma b2M concentrations (before and after HD) and contribution of the [redacted] column to b2M removal at each column size and blood-flow rate.
- Number of occurrences of visible thrombosis (clotting) in the [redacted] column, dialyzer, and/or tubing.
- Changes in plasma levels of complement factors, including total CH50, SC5b-9, and C5a.
- Changes in plasma levels of other proteins, including insulin, ACTH, IGFBP1, etc.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Inclusion Criteria

1. Males and females aged 40 – 75 years, inclusive.
2. ESRD requiring HD.
3. Dialysis vintage ≥ 24 months.
4. Absence of clinically-relevant residual renal function.
5. Regular HD sessions done at blood-flow rates between 400 and 500 mL/min, and with inter-dialysis intervals of 48 hours or more.
6. Stable health status for at least 4 weeks prior to screening based on medical history, and findings from physical examination, laboratory tests, vital signs, and ECG, as assessed by the investigator.
7. Life expectancy > 6 months (as determined by the investigator).
8. Body mass index (BMI) between 18 and 37 kg/m^2, inclusive, with a minimum body weight of 52 kg.
9. Must be on stable doses (> 4 weeks) of all treatments for concomitant diseases (e.g., diabetes, hypertension), but this does not apply to medications for conditions related to ESRD (e.g., medications for calcium and phosphate control, anemia).
10. Must be able to follow the study protocol and receive the treatment in the established timeframe.
11. Must provide a signed and dated informed consent form.

5.2. Exclusion Criteria

1. Patients for whom adequate anticoagulation cannot be achieved, such as those with severe anemia, severe hemorrhagic diathesis, severe gastrointestinal ulcers, or who are receiving anticoagulant medications for any reason other than as required for HD. Use of antiplatelet drugs (e.g., aspirin or clopidogrel) is allowed.
2. Patients for whom extracorporeal circulation therapy is contraindicated, such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute seizure disorder, or severe uncontrolled hypertension.
3. Patients with Kt/V < 1.2 during recent 8-week period prior to run-in.
4. History of hypersensitivity to heparin, including heparin-induced thrombocytopenia.
5. History of hypersensitivity to the [redacted] column or its components.
6. Patients who are not anticipated to be able to tolerate blood-flow rates of 450 mL/min during HD (e.g., new vascular access that cannot be used with 14G or 15G needles).
7. Patients who are at higher risk for IDH including:
    a. Medical records indicating the occurrence IDH (SBP < 90 mmHg) in more than 30% of HD sessions during a recent 8-week period prior to run-in;
    b. Patients requiring or expected to require extensive fluid management as determined by the investigator;
    c. Presence of pre-dialysis hypotension, defined as SBP < 90 mmHg and/or diastolic blood pressure (DBP) < 50 mmHg, before any of the last 3 dialysis sessions prior to screening;
    d. Diagnosis of IDH in medical records;

e. Diagnosis of autonomic dysfunction;
f. Patients who frequently require a UFR above 13 mL/kg/h.

8. Patients who are pregnant or breast-feeding or who are planning to become pregnant. Female subjects must not be pregnant or breastfeeding. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and prior to start of treatment. WOCBP and men must agree to use highly-effective contraception (Clinical Trial Facilitation Group 2014) prior to study entry. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her male partner is participating in the study, she should inform her treating physician immediately.
9. Clotting disorders.
10. Sickle cell anemia, hereditary spherocytosis, or autoimmune hemolysis.
11. Clinically significant abnormalities on screening ECG including QT interval corrected for heart rate (QTc) using Fridericia's correction formula [QTcF] of ≥ 500 ms in men and ≥ 520 ms in women.
12. Delirium (encephalopathy).
13. Out of range value for complete blood count (CBC), complete metabolic panel, or coagulation that the investigator deems clinically significant.
14. Thyroid stimulating hormone (TSH) below 0.2 or above 6.0 mIU/L, and/or clinically-relevant abnormalities in T3 or T4.
15. Hemoglobin level < 9.0 g/dL.
16. Alanine aminotransferase (ALT) and/or aspartate transaminase (AST) > 3 times upper limit of normal.
17. Uncontrolled type 2 diabetes.
18. Concurrent or have recent participation in another interventional clinical trial. Prior clinical trial subjects must have discontinued investigational agents/devices at least 30 days prior to planned first use of the [redacted] column.
19. History of severe depression/suicidality requiring hospitalization in the last 6 months.
20. Significant drug or alcohol abuse within the past 12 months.
21. Patients planning to receive renal transplantation during the study.
22. Patients with any other condition and/or situation the investigator believes may interfere with the safety of the subject during study participation, study conduct, or interpretation of study data.

5.3. Strategies for Recruitment and Retention

The Sponsor does not anticipate any specific challenges in meeting recruitment goals of enrolling and retaining a total of 12 evaluable subjects in this study. Approximately 15 subjects will be enrolled. Assuming a drop-out rate (unrelated to safety/tolerability) of 20%, enrollment at this level will yield approximately 12 evaluable subjects. Subjects will be recruited continuously until the planned sample size is achieved.

The estimated duration of subject participation of approximately 12 weeks is not expected to be challenging to subjects. Subjects will be compensated for the additional time required for study participation; details will be provided in the informed consent form.

5.4. Subject Withdrawal/Discontinuation

5.4.1. Reasons for Withdrawal/Discontinuation

A subject will be withdrawn from the study for the following medical or administrative reasons:

- Occurrence of an AE, including significant hemodynamic compromise, that represents an unacceptable risk to the subject and when continued participation in the investigational study is not warranted, in the judgment of the investigator, Sponsor, or medical monitor. The investigator must follow the subject until the AE resolves or is stable, unless the subject is lost to follow up.
- Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator.
- Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures.
- At the request of the subject (e.g., subject withdraws consent), investigator, Sponsor, or regulatory authority.
- Pregnancy.
- As subject will be discontinued if adequate dialysis is not achievable at a blood-flow rate of 250 mL/min during run-in.
- A subject will be discontinued if they have an SBP < 90 mmHg, confirmed by repeat measurement, before the start of an HD session.
- A subject will be discontinued if the number of IDH events (defined as an SBP < 90 mmHg, confirmed by repeat measurement) during a treatment period exceeds the predetermined threshold of the subject's Historical IDH Rate after de-escalation to the lowest column size (see Appendix 17.1).

5.4.2. Handling of Participant Withdrawals/Discontinuation

Subjects will be encouraged to complete the study and all assessments. Subjects may voluntarily withdraw at any time, and the investigator may discontinue individual subjects from the study at any time.

Approximately 15 subjects will be enrolled with the intent of obtaining 12 evaluable subjects (see Section 10.3).

Subjects who have received at least 1 HD with the [redacted] column but are withdrawn or withdraw from the study will be encouraged to complete the EOS procedures. The primary reason for study discontinuation will be documented on the case report form (CRF).

5.5. Premature Termination or Suspension of Study

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor and/or their representatives will arrange discontinuation procedures and notify the investigators, appropriate regulatory authority(ies), and IRB(s). In terminating the study, the Sponsor and the investigators will continue to protect the subjects' privacy and identity as required by relevant statutes and regulations.

Alkahest, Inc. has the right to terminate a study site from participating in the study at any time. Reasons for study or site termination may include, but are not limited to:

- Unanticipated risk to subject safety.
- Unsatisfactory subject enrollment.
- Unacceptable Protocol Deviations as assessed by the Sponsor's Program Physician.
- Inaccurate or incomplete data entry and recording/fabricated data.
- Investigational site non-compliance with ICH/GCP.
- Unacceptable emergent safety profile.

If the Sponsor were to receive withdrawal of IRB or FDA approval, or other action on the part of the IRB or FDA that affects the study, the Sponsor will notify the FDA and/or all reviewing IRBs, and all participating investigators, within 5 days of the IRB or FDA decision.

6. STUDY DEVICE

6.1. Study Device Description

[redacted]

6.1.2. Description, Appearance, Packaging, and Labeling

6.1.2.1. Device Description and Appearance

The [redacted] b2M apheresis column is an investigational device and may only be used for subjects who have been enrolled in the AKST1210-101 study and who are under the supervision of an appropriately qualified investigator.

[redacted]

[redacted]

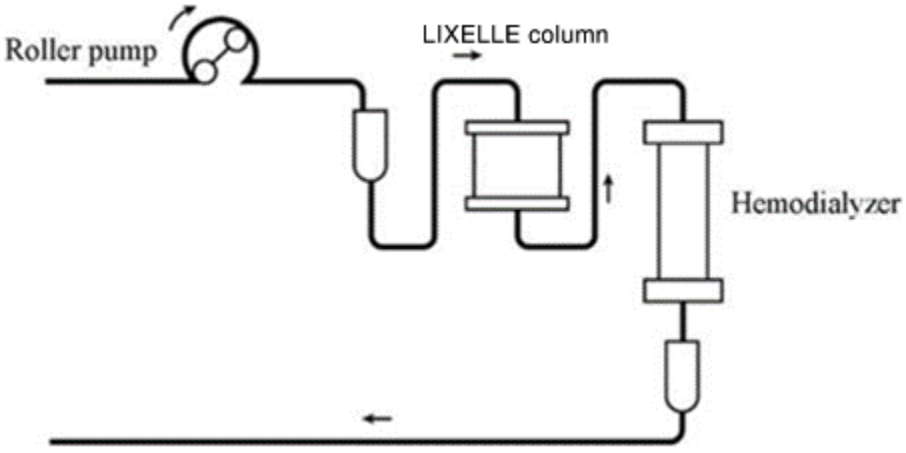
Table 2. Description of the [redacted] Column Model Sizes

Model	Column Capacity (mL)	Extracorporeal Volume (mL)
S-15	150	65
S-25	250	105
S-35	350	177

[redacted]

The [redacted] column is an extracorporeal column for adsorption of b2M from circulating blood, and it is placed in series with a hemodialyzer in an HD circuit. Figure 3 depicts the connection of the [redacted] column in the HD blood circuit.

Figure 3. [redacted] Column in the Hemodialysis Blood Circuit



6.1.2.2. Packaging and Labeling

The [redacted] column will be used and will not be modified in any way except for the addition of an Investigational Use label on the immediate package of the device with the appropriate investigational statement per 21 CFR 812.5(a): “CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use." An example of label text is provided below.

[redacted]

6.1.3. Product Storage

The [redacted] column should be handled with care during transportation and storage. The [redacted] column should be stored at temperatures between 5 °C and 30 °C. Direct sunlight, high humidity, excessive vibration, and freezing conditions should be avoided. Do not drop the [redacted] column or strike it with a hard instrument (e.g., forceps). Do not use any [redacted] column that has been damaged or frozen.

The fluid pathway of the [redacted] column is sterile and nonpyrogenic. Careful aseptic handling techniques are necessary to maintain this condition. Do not use the device if the package, the bag, or the product is damaged. Remove the device from the bag just before use.

6.1.4. Preparation

The [redacted] column will be connected in series before (upstream of) the dialyzer for the duration of each HD session. Specifics of column preparation (rinsing, priming, and disposal) are specified in the Device Procedures Manual.

6.1.5. Column Size Escalation and Administration

For a description of the [redacted] column escalation and administration for this study, please see Section 4.1 Description of the Study Design.

6.1.6. Duration of Therapy

The treatment period for each subject is approximately 6 weeks. The total duration of subject participation is expected to be approximately 8 to 12 weeks.

6.2. Study Device Accountability

Under the supervision of the investigator, qualified personnel are responsible for ensuring adequate accountability of all used and unused [redacted] columns. This includes acknowledgment of receipt of each shipment of [redacted] columns (quantity and condition), subject dispensing records, and destruction of used columns. [redacted] column dispensing records will document quantities received and quantities dispensed to subjects including the date dispensed, size of column (S-15, S-25, or S-35), lot number, subject's study identifier, initials of the individual responsible for dispensing, and initials of the dialysis nurse, or other qualified medical professional, administering the column. Device accountability will be monitored by a clinical research associate (CRA).

Accountability records must be maintained and readily available for inspection by representatives of Alkahest, Inc., or their designee, and are open to inspection by regulatory authorities at any time. Accounts of any [redacted] column accidentally wasted or intentionally disposed of must be maintained.

All unused [redacted] columns should be kept securely at the site until otherwise instructed. All unused containers of [redacted] columns at the site should not be returned or destroyed without prior written approval from the Sponsor, and authorized destruction must be performed in accordance with the site's or hospital's administrative policy (or equivalent), and/or relevant US regulations. The site's procedure(s) for disposal/destruction will be evaluated by the Sponsor or an authorized representative in order to ensure that it complies with study requirements. A copy of the site's device disposal policy should be maintained or referenced in the investigator's study file.

7. STUDY PROCEDURES AND SCHEDULE

7.1. Study Procedures/Evaluations

7.1.1. Study Specific Procedures

7.1.1.1. Screening and Run-in Procedures

During the screening visit, the following procedures will be performed:

- Informed consent
- Evaluation of inclusion/exclusion criteria
- Demographics
- Medical history and review of medications
- Assessment of HD history during a recent 8-week period, including blood-flow rates, vascular access, and IDH
- Physical examination, including measurements of height, weight, and BMI
- Vital signs
- 12-lead ECG
- Screening laboratory tests (including pregnancy test for WOCBP only)
- Concomitant medication review
- AEs should be collected and evaluated after the subject signs the Informed Consent; events that occur before signing of the Informed Consent should not be recorded as AEs

During the run-in period, the following procedures will be performed:

- HD (at maximum flow rate of 250 mL/min)
- Vital signs
- Targeted physical examination, including weight measurement before and after HD
- b2M/proteomic samples collected
- Laboratory tests (including pregnancy test for WOCBP only)
- Kt/V assessment
- Concomitant medication review
- AE evaluation/collection

Detailed descriptions of each of these procedures are provided in the sections immediately following. Information pertaining to the schedule of events during screening/run-in is provided in Section 15.1.

7.1.1.1.1. Demographics

Demographic information such as the subject's education level, ethnicity, and race will be collected.

7.1.1.1.2. Medical History and Review of Medications

The investigator or designee will obtain a detailed medical history through interview with the subject during screening. The medical history should focus on recent history. Additionally, the medical history should include:

- A detailed history of ESRD and HD in the last 6 months, including complications with vascular access, compliance with dietary and fluid restrictions, ability to maintain adequate levels, tolerability of HD, occurrence of IDH, blood-flow rates used, etc.
- Current/past illnesses and conditions
- Current symptoms of any active medical condition
- Surgeries and procedures
- Allergies

The investigator or designee should obtain a complete list of the subject's current medications, including over-the-counter drugs, herbal supplements, and/or vitamins, as well as those taken by the subject in the past 3 months and any regimen changes in the last 3 months. Any additions, discontinuation, or dosage changes in medication during the course of the study will be recorded.

7.1.1.1.3. Physical Examination

A complete physical examination will be performed at screening to assess the following organ systems: skin, ENT (ears, nose, and throat), head, eyes, lungs, heart, abdomen, musculoskeletal, extremities, and neurologic and lymphatic systems. Physical examination assessments performed within 3 months of the screening visit need not be repeated. Height will be measured at screening; weight will be measured at screening and BMI calculated. Weight will be measured throughout the study both prior to and after HD.

7.1.1.1.4. 12-Lead ECG

A 12-lead ECG will be performed after the subject has rested quietly for at least 5 minutes in a supine position. In some cases, it may be appropriate to repeat abnormal ECGs to rule out technical factors contributing to ECG artifacts or abnormality. It is important that leads are placed in the same positions each time for consistency. The overall conclusion with the interpretation of the ECGs will be recorded on the appropriate CRF. The interpretation of the ECGs will be recorded as normal, abnormal but not clinically significant, or abnormal and clinically significant. QTc will be calculated using Fridericia's correction formula.

7.1.1.1.5. Laboratory Evaluations

Blood samples will be collected and analyzed throughout the study. Blood will be drawn by a qualified medical provider. Laboratory evaluations will be completed by a central laboratory. Samples for screening laboratory evaluations should be collected either on a non-dialysis day or prior to HD. For additional information, refer to Section 15.3 Schedule of Laboratory Tests.

7.1.1.1.6. Hemodialysis

Beginning at run-in, HD will be conducted 3 times weekly at different blood-flow rates (see Section 4.1). The following key dialysis parameters will be captured during each HD treatment: arterial, venous, and transmembrane pressures every 30 minutes (from the HD machine; mmHg), mean and maximum blood flow rate (mL/min), reasons for changes in blood-flow rate, dialysis time (min), and type of dialyzer. Adequate safety precautions should be employed prior to and throughout HD, particularly for subjects who are at risk for developing IDH. Refer to Table 1 in

Section 2.2.1 for risks associated with the [redacted] column as well as proposed mitigation strategies.

7.1.1.1.7. Heparinization

The [redacted] column requires anticoagulation to prevent clotting, and the different column sizes generally require different amounts of heparin. Subjects will undergo heparinization according to institutional practices at the start of, and throughout, each HD session when the [redacted] column is used. The dose of heparin should be determined by the investigator based on each patient's individual requirements, the state of the dialysis circuit, and laboratory tests. Additional guidance is provided in the Device Procedures Manual.

7.1.1.2. Procedures to Assess Safety

Subjects enrolled in the trial will be monitored closely to assess safety and tolerability of the [redacted] column. Study-specific procedures that will be used for this purpose are summarized below. Information regarding the timing and frequency of these procedures is provided in Section 15:

- Review of AEs
- Vital signs
- Adequacy of dialysis
- Assessment of fluid status
- Targeted physical examination, weight measurements
- Laboratory assessments

7.1.1.2.1. Review of Adverse Events

Adverse events (AEs) will be reviewed, documented, and reported as required at each visit beginning at screening. For definitions, guidance, and additional information regarding AEs, please see Section 8.

7.1.1.2.2. Monitoring of Vital Signs

Vital signs monitoring will occur at every visit. Seated/reclined blood pressure (BP) will be recorded before each dialysis session, approximately every 30 minutes during dialysis, and at the end of the session. Other vital signs will be captured at the beginning and end of each visit; these include heart rate (beats per minute [bpm]), respiratory rate (breaths per minute), and body temperature. Vital signs will be measured after the subject has been seated/reclined for ~5 minutes.

Subjects will be monitored for IDH (see Definitions). Beginning at run-in, should the number of occurrences of IDH exceed a predetermined threshold based on the subject's Expected IDH Rate, then the subject will be discontinued or de-escalated to a previously tolerated, smaller column size at blood-flow rates up to 450 mL/min (Appendix 17.1).

7.1.1.2.3. Assessment of Fluid Status

Fluid status will be assessed during each HD treatment according to institutional standards of care. This will include body weight and assessment of pulmonary and dependent (pedal) edema and could include the following: pre and post HD bioimpedance, lung ultrasound monitoring of Kerley B-lines (Lichtenstein 2017), and continuous hematocrit monitoring during HD as deemed appropriate by the investigator/HD staff (Rodriguez 2005). Data will be collected concerning the performance of these procedures, as appropriate, and the outcomes assessed.

7.1.1.2.4. Targeted Physical Examination

A targeted physical examination (i.e., a re-examination of any abnormalities noted previously or new signs and symptoms that warrant clinical assessment) will be performed as needed (see Section 15). Weight will be assessed before and after HD at every visit.

7.1.1.2.5. Laboratory Evaluations

Blood samples will be collected and analyzed according to the schedule of laboratory tests (Section 15.3). Blood will be drawn by a qualified medical provider. Clinical laboratory evaluations will be processed by a central laboratory. Sites may collect and process these locally at the discretion of the investigator for ad-hoc safety monitoring and/or to guide heparin dosing.

7.1.1.2.6. Pregnancy Testing

Serum pregnancy testing will be performed in WOCBP in accordance with the Schedule of Events (see Section 15).

7.1.1.3. Procedures to Assess Device Performance

In addition to safety and tolerability, device performance will be assessed per the secondary endpoints defined in the study, including evaluation of change in plasma b2M concentrations (before and after HD) and contribution of the [redacted] column to b2M removal at each column size and blood-flow rate, number of occurrences of visible thrombosis (clotting) in the [redacted] column, dialyzer, and/or tubing, changes in plasma levels of complement factors, including total [redacted], as well as changes in plasma levels of other proteins, including [redacted].

7.1.1.3.1.

7.2. Laboratory Procedures/Evaluations

Blood samples will be collected for laboratory evaluations in accordance with Section 15.3 Schedule of Laboratory Tests. Screening and clinical laboratory evaluations will be processed by a central laboratory. Sites may collect and process laboratory evaluations locally at the discretion of the investigator for ad-hoc safety monitoring and/or to guide heparin dosing.

The investigator is responsible for determining and documenting whether out of range laboratory values are clinically significant. All clinically significant values will be recorded as AEs in the

CRF and followed until determined to be stable or resolved, unless the subject is lost to follow up. Once resolved, the appropriate CRF page(s) will be updated.

7.3. Study Schedule

7.3.1. Screening/Run-in

For a complete list of screening and run-in procedures and assessments, please see Section 15.1.

7.3.2. Treatment

For a complete list of treatment procedures and assessments, please see Section 15.1. and Section 15.2.

7.3.3. End of Treatment/End of Study Visits

For a complete list of end of treatment (EOT) and EOS procedures, please see Section 15.2.

7.3.4. Early Withdrawal

In the event of early withdrawal or discontinuation of a subject who has received at least 1 HD treatment with the [redacted] column, the EOS procedures will be performed unless the subject has withdrawn consent (also see Section 5.4).

7.4. Concomitant Medications

Concomitant medications taken by the subject during study participation will be recorded. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

7.5. Prohibited Medications, Treatments, and Procedures

The following concomitant medications, treatments, and procedures are prohibited:

- Anticoagulants other than those administered during HD. Use of antiplatelet drugs (e.g., aspirin or clopidogrel) is allowed.
- Anti-seizure medications for a seizure disorder.
- Concurrent or recent participation in another investigational clinical trial. Prior clinical trial subjects must have discontinued investigational agents at least 30 days prior to screening.
- Renal transplantation surgery.

8. ASSESSMENT OF SAFETY

8.1. Specification of Safety Parameters

8.1.1. Definition of Adverse Event, Procedure-Related Adverse Event, and Adverse Device Effect

Per the International Organization for Standardization (ISO) 14155:2011 an AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device.

- Note 1: This definition includes events related to the investigational medical device.
- Note 2: This definition includes events related to the procedures involved.
- Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

In relation to Note 2 above, a sub-classification of an AE is a procedure-related AE (PRAE). A PRAE is an AE that most likely occurs as a result of HD or related procedures, irrespective of the investigational medical device. Examples of a PRAE in HD include vascular access site complications, including access hemorrhage and venous needle dislodgement; disruption or contamination of the dialysis water system; venous air embolism; sepsis; cardiac complications including arrhythmia, angina, and cardiac arrest; electrolyte imbalances including hypokalemia and hyperkalemia, etc. In cases where relatedness is unclear, a conservative stance is to consider the event as related to the investigational medical device.

Per ISO 14155:2011, an ADE is an AE that is assessed as related to the use of an investigational medical device:

- Note 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

8.1.2. Definition of Serious Adverse Event and Serious Adverse Device Effect

Per ISO 14155:2011 a serious adverse event (SAE) is an AE that:

a. Leads to death.

b. Leads to serious deterioration in the health of the subject, that either results in:

- A life-threatening illness or injury, or
- A permanent impairment of a body structure or a body function, or
- Inpatient or prolonged hospitalization, or
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function.

c. Leads to fetal distress, fetal death, or a congenital abnormality or birth defect.

Per ISO 14155:2011 a serious adverse device effect (SADE) is an ADE that results in any of the consequences characteristic of a SAE.

All SAEs should be reported in the timeframe outlined in Section 8.4.

8.2. Classification of An Adverse Event

8.2.1. Severity of Event

Each AE/ADE must be assessed for its seriousness and severity. Severity will be assessed by the investigator or designee using the following definitions:

SEVERITY	DEFINITION
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE	Incapacitating with inability to work or do usual activity

Outcome will be assessed using the following categories: recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, fatal, or unknown.

8.2.2. Relationship to Study Device

Investigators are required to assess the relatedness (i.e., whether there is reasonable possibility that the study device caused the event) using the following definitions:

- Unrelated: another cause of the AE is more plausible, including AEs that commonly occur during HD (e.g. procedure-related AEs); a temporal sequence cannot be established with the onset of the AE and administration of the study device; or a causal relationship is considered biologically implausible.
- Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the study device, but the AE could also be attributed to concurrent or underlying disease, or the use of other devices or procedures. Possibly related should be used when the study device is one or several biologically plausible AE causes.
- Definitely Related: The AE is clearly related to use of the study device.

If either the investigator or the Sponsor considers the event related, then the event will be considered related for reporting purposes and will therefore be an ADE or SADE.

8.2.3. Expectedness of Adverse Device Effects

8.2.3.1. Unanticipated Adverse Device Effect

Per 21 CFR 812.3(s) 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."

The investigator is required to make an initial assessment of whether an SADE is considered anticipated according to the known risks and associated device effects identified in Section 2.2.1 and the Investigator's Brochure. If an SADE is considered unanticipated by the investigator, it must be reported to the Sponsor or designee according to the timeframes outlined in Section 8.4.2.1. Once received, the Sponsor or designee will be responsible for making the final determination of whether the device effect is unanticipated for subsequent reporting to FDA.

8.3. Time Period/Frequency for Event Assessment/Follow-up

At very clinic visit, subjects will be assessed for AEs and SAEs. All AEs and SAEs will be monitored and recorded by trained and knowledgeable personnel to protect subjects from harm. At the beginning of each visit, after the subject has had an opportunity to spontaneously mention any problems that may have occurred during the preceding interdialytic interval, the investigator should inquire about any possible interdialytic AEs by asking a non-leading question such as the following:

1. "How are you feeling?"
2. "Have you had any changes since your last assessment/visit?"
3. "Have you taken any new medicines since your last assessment/visit?"

During and for a period after each HD session, participating subjects will be closely monitored by qualified healthcare personnel who are trained in HD and who have experience in the types of AEs that typically occur during HD. Any events that occur during or after HD (before the subject leaves the clinic), will be assessed by the HD personnel (e.g. hemodialysis technician or nurse) and discussed as appropriate with the investigator or designee.

8.3.1. Post-Study Safety Assessment

The investigator is not obligated to actively seek safety information in former study subjects, but the investigator is encouraged to notify Alkahest, Inc. or their designee of any AE/ADE or SAE/SADE occurring within 30 days after a subject completes the study (or has their last visit) that the investigator judges may be reasonably related to study treatment or study participation.

8.4. Reporting Procedures

8.4.1. Adverse Event Reporting

All subjects who have given informed consent will be evaluated for AEs. All AEs that occur after initiation of treatment with the [redacted] column will be considered TEAEs. Subjects with TEAEs must be followed until the AE/ADE is resolved or is stable, unless the subject is lost to follow up.

Each AE/ADE must be described as follows: the date of onset, date of resolution, severity (mild, moderate, severe), frequency of the event (single episode, intermittent, continuous), action taken with study device (no action taken, device discontinued), outcome, relationship to study device* (unrelated, possibly related, definitely related), and seriousness criteria. Each AE/ADE must be recorded separately.

***Note:** Assessment of the relationship to study device will be made only when the AE occurs after the subject has initiated at least one (1) treatment with the [redacted] column. An AE occurring before the subject's exposure to the [redacted] column will always be labeled as "unrelated."

Any AE/ADE or SAE/SADE occurring during the study must be documented in the subject's source documentation and as an AE/ADE in the CRF. All SAE/SADEs should be reported to the Sponsor according to the reporting timeframes specified in Section 8.4.2.1.

The investigator should attempt to establish a diagnosis of the event (that meets the definition of an AE/ADE or SAE/SADE) based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/ADE and/or SAE/SADE and not the individual signs or symptoms. The diagnosis will become the basis for the verbatim term as reported by the investigator. If no diagnosis is known and clinical signs and symptoms are not present, the abnormal finding should be recorded.

In addition to the investigator's own description of the AE/ADE, each AE/ADE will be encoded according to the Medical Dictionary for Regulatory Activities (MedDRA). The investigator will take all appropriate and necessary therapeutic measures required for resolution of and AE/ADE. Any medication necessary for the treatment of an AE/ADE must be recorded on the concomitant medication CRF.

8.4.2. Serious and Unanticipated Adverse Events/Effects Reporting

8.4.2.1. Timeframes for Reporting

As per 21 CFR 812.150 an investigator shall submit to the Sponsor and to the reviewing IRB a report of any UADE (see Section 8.2.3.1) occurring during an investigation as soon as possible after the investigator first learns of the effect. Prompt notification of the Sponsor, and/or the Sponsor's representatives, and promptly providing requested follow-up information regarding such events is essential so that ethical and regulatory responsibilities and legal obligations can be satisfied. Investigators are responsible for reporting all SAEs (including SADEs and UADEs) according to the following timeframes:

- Initial notification (e.g., a completed SAE Report Form) and relevant source documents, if applicable, must be completed and faxed or emailed to [redacted] **within 24 hours** of observation or learning of the event.

- Follow-up information must be sent to the [redacted] **within 24 hours** of receipt of information by the investigational site.

All applicable events (including UADEs) must be reported to the IRB as soon as possible but in no event later than 10 working days after becoming aware of the event.

In addition to the IRB, the Sponsor will notify the FDA and all participating investigators in a safety report of potentially serious, unanticipated risks from clinical trials as soon as possible after the Sponsor receives the safety information and determines that the information qualifies for reporting:

- No later than 7 working days for events that are life threatening (in the opinion of the investigator or the Sponsor) or that involve death as an outcome.

- No later than 10 working days for all other UADEs.

Sites acting under their local IRB should submit all applicable events, unanticipated problems, and safety reports to their local IRB, if applicable. All safety reporting deviations should also be submitted to their local IRB, if applicable.

8.4.2.2. SAE/SADE/UADE Information to Report

The SAE Report Form must be completed and faxed or emailed according to the timeframes specified above. The submission should include copies of relevant source documents/medical records, if applicable. At a minimum, the SAE Report Form must contain the subject number, verbatim term, onset date, relationship to study device, and a brief narrative of the event. Please note that **relationship to study device as well as the reported verbatim term are very important** and should be included in the initial report as it may impact expedited regulatory reporting requirements for the event. The date of discovery by the site staff should be documented in the source documents.

A separate SAE Report Form should be used to report each SAE. However, if at the time of initial reporting, multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same SAE Report Form.

The investigator must record all relevant information regarding an SAE/SADE/UADE in the applicable sections of the report form, and the form must be signed by the investigator or his/her designee before transmittal to the Contract Research Organization (CRO) (see Section 8.4.2.1). It

is very important that the investigator provide his/her assessment of relationship to the study device as well as an applicable diagnosis at the time of the initial SAE report. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the appropriate SAE Report Form. However, there may be instances when copies of medical records for certain cases are requested by the CRO and/or the Sponsor. If medical records are submitted to the CRO, then all subject personal identifiers must be completely and thoroughly redacted prior to submission.

A blank SAE Report Form and instructions for reporting will be provided to the site and will be maintained in the investigator's study file.

If new information about an SAE/SADE/UADE is received or corrections to data are needed, the investigator should complete a new SAE Report Form and check the "follow-up" box on the form. This follow-up SAE Report Form should be submitted within 24 hours of learning of the information.

The SAE/SADE/UADE pages of the CRF should also be completed as thoroughly as possible.

8.4.3. Reporting of Pregnancy

While pregnancy itself is not considered an AE, pregnancy occurring in a clinical study must be followed to collect information regarding the experiences of gestation and pregnancy with study device exposure. The investigator must report any pregnancy that occurs in a female study subject or female partner of a male subject subsequent to first exposure to the study device until EOS, or within 3 months following a subject's last use of the device in the event of early termination. All pregnancies will be reported to the IRB, Sponsor, and CRO. In the event of a pregnancy, treatment will be discontinued, and the subject will undergo continued safety follow-up through pregnancy outcome.

Any pregnancy must be followed by the investigator until delivery or to the end of pregnancy. Any anomalies, complications, abnormal outcomes, or birth defect(s) observed in the child must be reported as an SAE within 24 hours of the investigator or study personnel's first knowledge.

8.5. Study Halting Rules

If any of the following safety events occur, a Safety Evaluation Meeting (defined below) will be triggered:

- Three or more SAEs (including SADEs and UADEs) that are assessed as possibly or definitely related to the study device by an investigator and confirmed as such by the Sponsor (see Section 8.2.2).
- An overall pattern of symptomatic, clinical, or laboratory events associated with the study device that the Sponsor's Program Physician or designee consider a serious potential safety concern (e.g., suspicious overall pattern).

Events that are not considered "device related" and will not contribute to the count of definitely-related SAEs that would trigger a Safety Evaluation Meeting.

Safety Evaluation Meeting

If safety events of potential concern occur during the trial (i.e., 3 related events or a suspicious overall pattern, as defined above) a Safety Evaluation Meeting will be triggered, and the study may be temporarily halted based on the observations. The Sponsor will inform investigators and the appropriate Regulatory Authorities in the event of any temporary halt in the study at any time during the conduct of the study. The purpose of the meeting is for investigators, the Sponsor, and the CRO Medical Monitor(s) to discuss and evaluate the safety of the subjects using available aggregated safety data.

Attendants at the Safety Evaluation Meeting will include the Program Physician of Alkahest (or his/her designee), the CRO medical monitor(s), and available active investigators participating in the trial. After sufficient data review, the Sponsor will choose one of the following courses of action:

1. Continue the study with no change to protocol.
2. Halt use of the [redacted] column (all column sizes/blood-flow rates) and stop the study.
3. Continue with a modified protocol design and amend the protocol as appropriate.

8.6. Safety Oversight

Safety oversight will be provided by the Sponsor's Program Physician or his or her designee and the CRO's Medical Monitor(s) in concert with the site investigators. There will be no formal Data Safety Monitoring Board established. As needed, Safety Evaluation Meetings will be convened as described in Section 8.5 to monitor the ongoing safety of the study. The Sponsor's Program Physician or designee is the final authority for safety oversight in the study.

9. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and wellbeing of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the study CRO in accordance with the Clinical Monitoring Plan (CMP).

- Details of clinical site monitoring tasks and scope are documented in the study's CMP. The CMP describes in detail who will conduct monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

- Co-monitoring visits and/or independent audits may be conducted by the Sponsor in accordance with a quality oversight plan or equivalent to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Design Model and Analytical Plans

Data from this feasibility study will be analyzed mostly in a descriptive manner. Limited statistical comparison of outcomes across the various column-size and blood-flow-rate combinations will be performed. With the limited sample size, exact methods for binomial data and t-statistics for continuous data will be used in generating 95% confidence intervals for estimates. A statistical analysis plan (SAP) will be prepared to provide details of the analysis of data. Counts and percentages of safety events will be reported separately for each combination. Similarly, continuous safety data will be summarized by combination.

No formal statistical comparison of the safety data will be performed. The rate of IDH in the general ESRD population, using the Nadir 90 definition, is 10%, based on a study in over 10,000 US patients undergoing HD (Flythe 2015). With 12 subjects there will be an approximate 70% probability of detecting at least 1 event in each week. Descriptive statistics will be utilized for trial conduct: screen failures, enrollment, withdrawal of consent, and study completion. Primary and secondary endpoints will be assessed at the beginning and end of each week of treatment for a particular column size and blood-flow rate combination. The effect of blood-flow rate will be assessed for a given column size as well as intrasubject and across-subject variability. The sample size was chosen based on clinical consideration of the study designed to test the safety and functionality of the [redacted] column operated at higher blood-flow rates.

10.2. Statistical Hypotheses

The primary objective of the study is to evaluate the safety and tolerability of the [redacted] column when used at blood-flow rates up to 450 mL/min. The safety and tolerability will be assessed at each column size and blood-flow rate to enable comparisons across those variables in each subject (intrasubject) and across all subjects.

10.3. Analysis Datasets

Two (2) analysis datasets will be defined as follows:

- Safety Dataset: all subjects who received at least 1 (or partial) HD treatment with the [redacted] column.
- Evaluable Dataset: all subjects who complete blood-flow rates up to 450 mL/min for at least 1 column size (e.g., S-15 at 250 and up to 450 mL/min).

The presentation of baseline characteristics will be conducted on the Safety Dataset. Comparison of the safety and tolerability of each column size and blood-flow rate will use both the Safety Dataset and Evaluable Dataset.

10.4. Description of Statistical Methods

10.4.1. General Approach

Using the safety dataset, all safety endpoints will be summarized serially over time using descriptive statistics to assess the within-subject changes and between-condition differences. Overall baseline and demographic data will be summarized using descriptive statistics.

For analysis of the primary and secondary endpoints, the following will be considered:

- For endpoints that are continuous in nature:
  - Number of observations, mean, median, minimum and maximum, and standard deviation (SD) and change from baseline values (or percent change from baseline) will be presented as descriptive summary.
- For endpoints that are categorical in nature:
  - Frequency counts and percentages will be presented as descriptive summaries.

Subject disposition (e.g., the number of subjects enrolled, completed, and discontinued at each phase) will be summarized, and medical history data will be listed. Prior and concomitant medications taken from screening and during the study will be categorized by World Health Organization classification for therapeutic class and medication name, listed and summarized by number and percentage of subjects.

Final analyses are not limited to the summaries described herein. As noted above, analytical details and assumptions will be fully presented in the SAP.

10.4.2. Analysis of the Primary Endpoint

Safety and tolerability will be evaluated by examining the occurrence of TEAEs and AEs leading to de-escalation and/or discontinuation from the study and by the number of subjects who are able to complete each phase (i.e., a column size at both blood-flow rates).

Summary tabulations of the reported AEs will be presented by column size after the verbatim terms have been coded to preferred terms (PTs) and system organ classes (SOCs) using the MedDRA Version 23.0 coding dictionary or higher. The summaries will include severity and attribution to the study device. Multiple reports of the same AE by the same subject will be counted only once at the highest severity and strongest attribution to the study device.

10.4.3. Analysis of the Secondary Endpoints

Actual values and changes from baseline in clinical laboratory measurements will be assessed and summarized. Laboratory shift tables or graphics displaying the change (number of subjects) relative to the reference range from baseline to each study visit may also be presented for each test. The investigator should exercise his or her medical and scientific judgment in deciding and

documenting whether an abnormal laboratory finding, or other abnormal assessment, is clinically significant.

For secondary endpoints that are continuous in nature the mean, median, minimum, maximum, and standard deviation will be summarized.

For secondary endpoints that are categorical in nature, the frequency counts and percentages will be presented as descriptive summaries.

Per-subject extent of exposure will be listed.

10.4.4. Adherence and Retention Analyses

Subject adherence with the study visits schedule, visit procedures, HD procedures, and subject retention will be assessed. Subject adherence will be assessed for each column size and blood-flow rate. Reasons for study discontinuation will be compared across column-sizes and blood-flow rates and across subgroups of interest, as appropriate.

10.5. Sample Size

The sample size for this study was based on FDA Guidance for the Content for Premarket Notifications for Conventional and High Permeability Hemodialyzers (FDA 1998) which recommends that data be collected for a minimum of 12 subjects for a minimum of 36 treatments. In this study, approximately 15 subjects between 40 and 75 years of age with ESRD will be enrolled. Assuming a drop-out rate of 20% (unrelated to safety) enrollment will yield approximately 12 evaluable subjects. With regard to the most important risk of [redacted] IDH, a sample of 12 subjects will provide approximately 70% probability of detecting at least 1 IDH event in each week (i.e., for each column size and blood-flow rate combination). This estimate is based on the assumption that the rate of IDH in the general ESRD population, using the Nadir 90 definition, is 10%, based on a study in over 10,000 US patients undergoing HD (Flythe 2015).

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 R2 and regulatory and Institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of regulatory agencies, the IRB, the Sponsor, or the Sponsor's representatives to examine (and when permitted by applicable law, to copy) clinical records for the purposes of QA reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subject's memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being attributable, legible, accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

It is not acceptable for the CRF to be the only record of a subject's participation in the study. This is to ensure that anyone who would access the subject's medical record has adequate knowledge that the subject is participating in a clinical trial. Source document templates will be developed for this study.

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1. Ethical Standard

The investigator will ensure this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in, 21 CFR Parts 11,50, 54, 56, 812, ICH E6 R2, and the Declaration of Helsinki.

12.2. Institutional Review Board

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB. Approval from the IRB must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval.

All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented subjects need to be re-consented.

Any modifications or amendments to the protocol must also be submitted to the IRB for approval prior to implementation.

If the investigator were to receive withdrawal of IRB approval, or other action on the part of the IRB that affects the study, the investigator will provide written notification within 5 days of the IRB decision to the Sponsor. If Alkahest were to receive withdrawal of IRB approval, or other action on the part of the IRB that affects the study, the Sponsor will provide written notification within 5 days of the IRB decision to the FDA and investigators.

12.3. Informed Consent Process

12.3.1. Consent Forms

Consent forms describing in detail the study device, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to any study-related procedures.

12.3.2. Consent Procedures and Documentation

It is the responsibility of the investigator or designee to obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures.

Subjects should have the opportunity to discuss the study with their family members or other advisors and the time to consider participation in the trial carefully. Subjects may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subjects will

be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The investigator or designee must utilize an IRB approved consent form that contains the elements required by ICH GCP and applicable regulatory requirements for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person obtaining consent. A copy of the signed consent form will be provided to the subject. By signing the informed consent form, all parties agree they will complete the evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (e.g., date of screening).

All subjects who provide consent will be assigned a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to the study subject. Once a number is assigned to a subject, that number will remain with that study subject and will not be reused.

If an individual's medical chart or results of diagnostic tests performed as part of an individual's regular medical care are going to be used for screening, written informed consent must be obtained prior to review of that information in accordance with Health Insurance Portability and Accountability Act.

12.4. Participant and Data Confidentiality

Subject confidentiality is held in strict trust by the participating investigators, their staff, the Sponsor, and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB, or government regulatory agencies may inspect documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. An identification code (i.e., not names) should be recorded on non-local laboratory samples, requisitions, and any documents submitted to the CRO, Sponsor, and/or IRB. The investigator must keep a subject log showing codes, names, and pertinent contact information for all subjects screened and for all subjects enrolled in the trial. The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and/or Institutional regulations.

12.5. Future Use of Stored Specimens

With the subject's approval and as approved by local IRBs, de-identified biological samples may be stored at Alkahest, or designee, for future use. These samples could be used for future research and to improve treatment. Alkahest will also be provided with a code-link that will allow linking the biological specimens with the specific data from each subject, maintaining the masking of the identity of the study subject. Subjects may choose whether the Sponsor can store and use samples for further research.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research.

When the study is completed, access to study data and/or samples will be managed by Alkahest. In the event Alkahest transfers ownership to another commercial Sponsor, ownership of the samples may be transferred as well.

13. DATA HANDLING AND RECORD KEEPING

13.1. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data reported.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL. The investigator may need to request previous medical records or transfer records, depending on the trial; also, current medical records must be available.

The CRF must be completed in a timely manner. The investigator will review and approve the CRF for each study subject after all data have been entered, the CRFs have been source document verified, and all queries have been resolved. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of an AE, thorough efforts should be made to clearly document the outcome.

13.1.1. Investigator Responsibilities

The investigator will comply with the protocol (which has been approved/given favorable opinion by an IRB), ICH GCP, and applicable regulatory requirements. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the Sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

13.1.1.1. Reporting Responsibilities

Investigators are required to:

- Submit AEs/ADEs/SAEs/SADEs/UADEs to the study Sponsor or designee, as per the reporting requirements outlined in Section 8.4.
- Submit to their IRB a report of any UADEs, or events of subject death, occurring during an investigation as soon as possible but in no event later than 10 working days after the investigator first learns of the event.
- Notify the study Sponsor of withdrawal of IRB approval or other action on the part of the IRB that affects the study as soon as possible but in no event later than 5 working days.

- Notify the Sponsor, Monitor, and IRB of study progress at regular intervals but in no event less often than yearly.
- Notify the Sponsor/IRB of any significant deviations from the investigational plan for emergency purposes, as soon as possible but in no event later than 5 working days after deviation occurs to protect the life or physical well-being of a subject in an emergency.
  - For non-emergency purposes, obtain prior approval by Sponsor and, if deviation may affect scientific soundness of the trial or the rights, safety, or welfare of subject, also obtain approval by the IRB and FDA as an Investigational Device Exemption (IDE) supplement.
- Notify the Sponsor and IRB if a subject is treated with an investigational device without first obtaining informed consent, within 5 working days of use of the investigational device.
- Notify the Sponsor and IRB with a final study report within 3 months after termination or completion of study or termination of site's participation.

13.1.2. Study Files

Investigators are required to maintain on file the following accurate, complete, and current records relating to this study:

- All correspondence relating to the study with another investigator, an IRB involved in the study, Alkahest, Inc., a monitor, or FDA, including required reports.
- Records of receipt, use, or disposition of a [redacted] column.
- All clinical forms and documentation, including:
  - Records of each subject's case history and exposure to the [redacted] column.
  - A copy of the signed subject consent form.
  - Date and time of exposure to the [redacted] column.
  - All procedure and follow-up report forms, including supporting documents.
  - Records of any adverse event or device effect, including supporting documentation.
  - Records pertaining to subject deaths during the study.
  - The study protocol/amendments including documentation and rationale for any deviations from the clinical protocol.
  - Any other records required by Alkahest, Inc. or FDA.

The investigator's study file will contain all of these documents, as well as staff curriculum vitae and authorization forms, and other appropriate documents and study-specific manuals (e.g., Device Procedures Manual).

13.2. Study Records Retention

Per 21 CFR 812.140(d), an investigator or Sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following 2 dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application, a notice of completion of a product development protocol, a humanitarian device exemption application, a premarket notification submission, or a request for De Novo classification.

Before the investigator destroys any material related to the clinical study, he/she must obtain approval in writing from the Sponsor.

The investigator should keep a file where the full name and address of the subject and all signed informed consents are included for at least 15 years after completion of the trial. Any original study-related information that permits verification of inclusion and exclusion criteria, including clinical history, a copy of all data collection logs, and documents on the use of the study device, must be stored for as long a time period as permitted by the center.

Should the investigator wish to move study records to another location, arrangements must be made to store these in sealed containers so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

13.3. Protocol Deviations

A Protocol Deviation is any noncompliance with the clinical trial protocol or with GCP. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. When deviations occur, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol Deviations will be categorized as either Major or Minor and will be defined in the study specific Protocol Deviation Plan.

> **Major Protocol Deviations** are departures from the approved protocol relating to the conduct of the study which may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect the rights, safety, and/or wellbeing of study participants. Examples of Major Protocol Deviations include, but are not limited to:
>
> - Failure to obtain informed consent (i.e., no evidence of informed consent)
> - Enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population
> - A device dispensing or related error that could have affected the safety of the subject
> - Failure to collect data necessary to interpret the primary endpoint(s), as this may compromise the scientific value of the trial.

Major Protocol Deviations may result in data that are not deemed evaluable for analysis and/or may require that subjects are discontinued from the study.

Note: Observations categorized as Major may include those situations where there is a pattern of deviation, numerous Minor observations, or other significant deviation.

Minor Protocol Deviations are departures from the approved protocol relating to the conduct of a study that does not affect the rights, safety, and/or wellbeing of study participants or the study outcomes or data quality. Examples of Minor Protocol Deviations include, but are not limited to:

- A protocol visit date outside of a visit window
- An isolated case of a missed or incomplete study procedure
- An isolated incident of a missed or incomplete study evaluation

Minor Protocol Deviations would not generally preclude subject data from the *per protocol* analysis population. Observations categorized as Minor may become Major if not corrected.

All deviations will be logged and tracked by the site and CRO. Periodic review of Protocol Deviations will serve an indicator of site performance.

Per 21 CFR 812.150(a)(4), it is the responsibility of the site to use continuous vigilance to identify and report deviations promptly (within 5 working days) to the study CRO and/or Sponsor. All deviations must be addressed in study source documents. Notification of Protocol Deviations must be sent to the local IRB per their guidelines. The site investigator/study staff is responsible for knowing and adhering to their IRB requirements.

13.4. Publication and Data Sharing Policy

In compliance with the International Committee of Medical Journal Editors clinical trials registration policy and Section 801 of the FDA Amendments Act of 2007, this study will be registered by the Sponsor in ClinicalTrials.gov, a public trials registry which is sponsored by the National Library of Medicine.

Notwithstanding the Sponsor's requirements for registration and data sharing in ClinicalTrials.gov, any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the investigator(s) and the Sponsor. In the case of multicenter studies, it is mandatory that the first publication be made based on the totality of data obtained from all centers, analyzed as stipulated in the protocol, and presented and interpreted as documented in the final Clinical Study Report. The resulting publication will name investigators according to the policy of the chosen journal. Where it is not permitted for all investigators to be included as authors, the publication will name all investigators within the publication.

Individual investigators may publish data arising from their own subjects. The investigator will provide the Sponsor with copies of written publications (including abstracts and posters) at least 60 days in advance of submission. This review is to permit the Sponsor to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential information is not inadvertently divulged (including patent protection), to allow adequate input or supplementary information that may not have been available to the investigator, and to allow establishment of co-authorship.

Investigators participating in multicenter studies must agree not to engage in presentations based on data gathered individually or by a subgroup of centers before publication of the first main publication unless this has been agreed otherwise by all other investigators and the Sponsor. However, in the event that no publication of the overall results has been submitted after approval of the Clinical Study Report, investigators may publish results of one or more center's subjects to the same review as outlined above. The Sponsor will circulate proposed multicenter publications to all investigators for review.

Data will be reviewed by all participating investigators prior to publication. The study Sponsor will have 90 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 30 days to review all abstracts.

14. FINANCIAL DISCLOSURE AND CONFLICT OF INTEREST POLICY

A separate financial disclosure agreement will be made between each principal investigator and Alkahest, Inc. or its authorized representative before the study agent is shipped. Each investigator will notify Alkahest, Inc. or its authorized representative of any relevant changes during the conduct of the study and for 1 year after the study has been completed. Alkahest and the study CRO will evaluate any disclosed conflicts of interest and will establish a mechanism for their management.

15. SCHEDULE OF EVENTS

15.1. Screening (Weeks -5 to -2)/Run-in (Week -1)/Treatment Period (Weeks 1 and 2)

	Screening	Run-In Period			Treatment Period					
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Study Week	Weeks -5 to -2	Week -1			Week 1*			Week 2		
Study Day(s) (± 1)	Days -35 to -7	Day -6	Day -3	Day -1	Day 1	Day 3	Day 6	Day 8	Day 10	Day 13
Procedures										
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history	X									
Physical examination	X									
12-lead ECG	X									
Targeted physical examination		X	X	X	X	X	X	X	X	X
Height/BMI	X									
Weight	X	X	X	X	X	X	X	X	X	X
Vital signs[1]	X	X	X	X	X	X	X	X	X	X
Laboratory tests[2]	X		X	X		X	X		X	X
Column size	None	None			S-15			S-15		
Hemodialysis blood-flow rate (mL/min)	Standard rate	250						Up to 450		
Assessment of fluid status		X	X	X	X	X	X	X	X	X
Kt/V assessment			X			X			X	
Adverse events and concomitant medications	X	X	X	X	X	X	X	X	X	X

*The first treatment with the [redacted] column S-15 (150 mL) will occur mid-week (e.g., on Wednesday for subjects on a Monday/Wednesday/Friday schedule and on Thursday for subjects on a Tuesday/Thursday/Saturday schedule).

1. For additional information, see Section 7.1.1.2.2 Monitoring of Vital Signs.
2. For additional information, see Section 15.3 Schedule of Laboratory Tests.

15.2. Treatment Period (Weeks 3 to 6) /End of Study (Week 7)

	Treatment Period												EOS
Visit Number	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22 (EOT)	V23
Study Week	Week 3*			Week 4			Week 5*			Week 6			Week 7
Study Day(s) (± 1)	Day 15	Day 17	Day 20	Day 22	Day 24	Day 27	Day 29	Day 31	Day 34	Day 36	Day 38	Day 41	Day 43
Procedure													
Physical examination													X
12-lead ECG													X
Targeted physical examination	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests[2]		X	X		X	X	X	X	X	X	X	X	X
Column size	S-25						S-35						
Hemodialysis blood-flow rate (mL/min)	250			Up to 450			250			Up to 450			
Assessment of fluid status	X	X	X	X	X	X	X	X	X	X	X	X	
Kt/V assessment		X			X			X			X		
Adverse events and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X

*The escalation to the subsequent column-size and flow-rate combination of the [redacted] column will occur mid-week (e.g., on Wednesday for subjects on a Monday/Wednesday/Friday schedule and on Thursday for subjects on a Tuesday/Thursday/Saturday schedule).

1. For additional information, see Section 7.1.1.2.2 Monitoring of Vital Signs.
2. For additional information, see Section 15.3 Schedule of Laboratory Tests.

15.3. Schedule of Laboratory Tests

Assessment	Screening	Run-in			Treatment Period																	End of Study (EOS)
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22 (EOT)	V23
b2M/proteomics				X			X			X			X			X			X			X	X
Serum pregnancy (WOCBP only)	X			X																			X
Hematology	Note: CBC, Hp, Hgb, and plasma-free Hgb should be taken AFTER HD V4-V21.																						
Complete blood count (CBC)	X					X			X									X			X		
Haptoglobin (Hp)				X		X			X									X			X		
Hemoglobin (Hgb)	X					X			X									X			X		X
Plasma-free Hgb				X		X			X									X			X		
Chemistry	Note: BUN and Creatinine should be collected BEFORE and AFTER HD.																						
Alanine aminotransferase (ALT)	X											X											
Albumin	X											X											
Aspartate transaminase (AST)	X											X											
Bicarbonate (HCO_3)	X											X											
Bilirubin (total)	X											X											
Blood urea nitrogen (BUN)	X		X			X			X			X			X			X			X		
Calcium (Total)	X						X															X	
Chloride (Cl)	X											X											
Creatine kinase (CK)	X																						
Creatinine	X		X			X			X			X			X			X			X		
Glucose	X						X					X										X	
Hemoglobin A1c (HbA1c)	X																						

Assessment	Screening	Run-in			Treatment Period																		End of Study (EOS)
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22 (EOT)	V23
Lactate dehydrogenase (LDH)	X																						
Magnesium (Mg)	X																						
Potassium (K)	X											X											
Phosphate	X											X											
Protein (total)	X											X											
Sodium (NA)	X											X											
Coagulation																							
Activated partial thromboplastic time (aPTT)	X											X											
Prothrombin time (PT/INR)	X											X											
Serology																							
Hepatitis B surface/core antigen (HBsAg)	X																						
Hepatitis C antibody (HCV Ab)	X																						
Human immunodeficiency virus antibody (HIV Ab, HIV1/HIV-2)	X																						
Other Clinical Labs	Note: All labs in the "Other Clinical Labs" section should be collected AFTER HD at V4.				Note: All labs in the "Other Clinical Labs" section should be collected BEFORE and AFTER HD at V7 and V22.																		
Adrenocorticotropic hormone (ACTH)				X			X															X	
Complement (total)(CH50)				X			X															X	
Complement C3 and C4				X			X															X	
Complement C5a				X			X															X	
Gastrin				X			X															X	
Heparin Anti-Xa			X			X			X			X			X		X			X			X

Assessment	Screening	Run-in			Treatment Period																	End of Study (EOS)
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22 (EOT)	V23
(only for patients on low molecular weight heparin)																							
Insulin				X			X															X	
Insulin-like growth factor-binding protein 1 (IGFBP1)				X			X															X	
Osteocalcin				X			X															X	
Parathyroid hormone (PTH)				X			X															X	
Terminal complement complex (sC5b-9)				X			X															X	
Thyroid-stimulating hormone (TSH)	X						X															X	

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17. APPENDICES

17.1. Escalation, De-escalation, and Discontinuation Rules for Treatment with the [redacted] Column

The purpose of the escalation rules is to ensure the safety of the subject when transitioning to a larger-size column. Since the main risk of [redacted] – IDH – is related to column size, the occurrence of IDH will be the main criterion used to determine the appropriateness of escalation to a larger column size; however, other factors will be considered when escalating, including the overall status of the subject, other AEs, laboratory abnormalities, adequacy of HD, etc.

The following definitions are relevant to evaluating whether to escalate, de-escalate, or discontinue a subject:

- ***Intradialytic hypotension/hypotensive (IDH) event***: An SBP < 90 mmHg confirmed by repeat measurement.
- ***Expected IDH Rate****:* The expected number of occurrences of IDH per weekly treatment period used to assess escalation, de-escalation, and discontinuation. Expected IDH Rate is derived from a subject's Historical IDH Rate (see table below).
- ***Historical IDH Rate***: The number of occurrences of IDH as documented in a subject's medical record during a recent 8-week period prior to the run-in period. Subjects with 7 or more IDH events during this 8-week interval will be excluded.

Table 3 below provides the corresponding Expected IDH Rate based on the Historical IDH Rate and summarizes the rules for escalation, de-escalation, or discontinuation based on the number of occurrences of IDH.

Table 3. Guidance for Escalation, De-escalation, and Discontinuation Based on IDH Rate

Historical IDH Rate over 8 Weeks	Expected Weekly IDH Rate	Escalate to Next Column Size or Blood-Flow Rate if IDH Rate in 1 Week is:	De-escalation to Previous Treatment or Discontinue from Study if IDH Rate in 1 Week is:
0	< 1	0	> 1
1	< 1	1 or less	
2	< 1		
3	< 1		
4	< 1		
5	< 1	2 or less	> 2
6	~1		

17.1.1. Escalation Rules

A subject may be escalated to the next larger column size or next blood-flow rate if they experience no more than the number of IDH events described in Table 3, maintain an Hgb level ≥ 9 g/dL, and have no other safety signals that the investigator believes could put the subject at risk. If a subject has an SBP < 90 mmHg, confirmed by repeat measurement, *before* the start of

HD, the subject will be withdrawn from the study because this constitutes significant hemodynamic compromise.

If a subject cannot attain the planned high blood-flow rate (450 mL/min) due to technical factors (e.g. differential pressures in the dialysis circuit), the investigator can adjust the blood-flow rate down to such a rate that allows the [redacted] column to be tested at a higher rate than 250 mL/min.

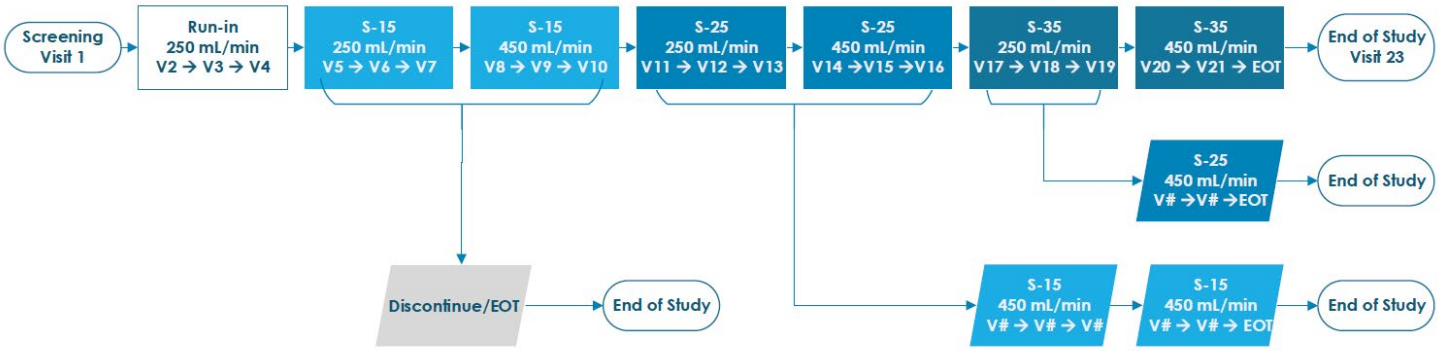
17.1.2. De-escalation Rules

The purpose of the de-escalation rules is to ensure the safety of a subject who is experiencing IDH, anemia or other safety issues that may be related to the column size.

A subject should be de-escalated if during the 1-week treatment period they experience the number of IDH events described in the table above and/or have an Hgb level < 9 g/dL despite receiving optimized treatment with ESA.

De-escalation will only be applicable at V11 through V19 as shown in Figure 4 below. Subjects who do not tolerate treatment with the S-15 column at any time prior to V11 or after V19 will be discontinued (see Section 17.1.13. Discontinuation Rules).

Figure 4. De-escalation Schematic



Subjects will continue with the same visit schedule after de-escalation. At the visit following confirmation of de-escalation, treatment will resume with the previous column size at the high flow rate (up to 450 mL/min).

- If de-escalation occurs during V11 through V16, subjects will resume treatment at the next scheduled visit with the S-15 column at up to 450 mL/min and will continue with this column size/flow rate combination through EOT (V22).
- If de-escalation occurs during V17 through V19, subjects will resume treatment at the next scheduled visit with the S-25 column at up to 450 mL/min and will continue with this column size/flow rate combination through EOT (V22).

Table 4 below illustrates the visit schedule for subjects who de-escalate. ***Note***: the only change compared to Section 15 is column size and flow rate.

Table 4. Schedule of Events for Subjects Who De-escalate

	Treatment Period												EOS
Visit Number	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22 (EOT)	V23
Study Week	Week 3			Week 4			Week 5			Week 6			Week 7
Study Day(s) (± 1)	Day 15	Day 17	Day 20	Day 22	Day 24	Day 27	Day 29	Day 31	Day 34	Day 36	Day 38	Day 41	Day 43
Procedure													
Physical examination													X
12-lead ECG													X
Targeted physical examination	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests[2]		X	X		X	X	X	X	X	X		X	X
Column size	S-15						S-15 OR S-25 (if de-escalated after V16)						
Hemodialysis blood-flow rate (mL/min)	Up to 450												
Assessment of fluid status	X	X	X	X	X	X	X	X	X	X	X	X	
Kt/V assessment		X			X			X			X	X	
Adverse events and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X

1. For additional information, see Section 7.1.1.2.2 Monitoring of Vital Signs.
2. For additional information, see Section 15.3 Schedule of Laboratory Tests.

17.1.3. Discontinuation Rules

Subjects will be discontinued and complete the End of Study visit procedures if:

- Subject does not tolerate the S-15 column at either flow rate
- Subject does not tolerate the S-35 at the higher flow rate (up to 450 mL/min)
- Subject has already de-escalated and they experience the number of IDH events described in the Table 3 and/or have an Hgb level < 9 g/dL despite receiving optimized treatment with ESA
- At any time during the study at the investigator's discretion

As a reminder, all occurrences of IDH after the time of consent will be recorded as AEs.

18. REVISION HISTORY

18.1. Summary of Changes

Protocol Version 2.1 dated 13MAY2021
Replaces: Protocol Version 2.0 dated 12APR2021

The following table describes changes from Version 2.0 (dated 12APR2021) with justifications provided.

Section(s)	Description	Justification
Throughout	Protocol version update. ***Previously read**:* "V2.0_12APR2021" ***Now reads**:* "V2.1_13MAY2021"	Version control.
[redacted]	[redacted]	[redacted]
7.1.1.2.2	The following content was removed: "If screening and/or EOS occur on a day in which a subject is not receiving HD, vital signs will be measured after the subject has been seated/reclined for ~5 minutes."	The proposed language regarding measurement of vital signs at screening and EOS caused confusion; therefore, the content was removed.
13.4	The following text was reinstated: "In compliance with The International Committee of Medical Journal Editors clinical trials registration policy and Section 801 of the FDA Amendments Act of 2007, this study will be registered by the Sponsor in ClinicalTrials.gov, a public trials registry which is sponsored by the National Library of Medicine. Notwithstanding the Sponsor's requirements for registration and data sharing in ClinicalTrials.gov,"	This Phase 1 study meets criteria for publication on ClinicalTrials.gov; therefore, Alkahest will add this study to the ClinicalTrials.gov registry.

Protocol Version 2.0 dated 12APR2021
Replaces: Protocol Version 1.2 dated 06JAN2021

The following table describes changes from Version 1.2 (dated 06JAN2021) with justifications provided.

Section(s)	Description	Justification
Throughout	Protocol version update. ***Previously read**:* "V1.2_06JAN2021"	Version control.

	Now reads: "V2.0_12APR2021"	
Throughout	Minor grammar, content, and style updates.	Minor content updates for clarity/accuracy/style of content.
Table of Contents	Minor content updates.	Minor updates required to reflect revised content.
List of Definitions, 17.1	The Definition of Historical IDH Rate has been revised as follows: ***Previously read:*** *"*The number of occurrences of IDH as documented in a subject's medical record during a recent 8-week period prior to enrollment." ***Now reads:*** "The number of occurrences of IDH as documented in a subject's medical record during a recent 8-week period prior to the run-in period."	Clarification that the Historical IDH Rate begins prior to the run-in period rather than enrollment.
Protocol Summary (Précis, Population), 4.1, 5.1, 10.5	The subject age range was previously 45-70 years; it has been changed to 40-75 years.	Revised to expand recruitment.
Protocol Summary (Précis), 4.1, 15.1, 15.2, 17.1.2 (Table 4)	The run-in period will now be considered Week -1 of the study. Treatment with the [redacted] column will begin in Week 1. Previous and subsequent study weeks/days have been renumbered, as appropriate, throughout the document.	For the purposes of accurate data collection, the run-in period will be considered Week -1, with [redacted] column treatment beginning at Week 1.
Protocol Summary (Précis), 4.1, 15.1, 15.2	Content was added to clarify that the first treatment with the [redacted] column S-15 will occur mid-week (e.g., on Wednesday for subjects on a Monday/Wednesday/Friday schedule and on Thursday for subjects on a Tuesday/Thursday/Saturday schedule).	Clarification of treatment weekly treatment schedule.
Protocol Summary (Précis), 2.2.1 (Table 1)	Minor modifications to the risk mitigation strategies for IDH including: • Supine positioning/lower limb elevation. • Avoidance of changes in medications, especially those that can affect BP, during the study.	Clarification and provision of additional mitigation strategies for IDH.
Protocol Summary (Number of Sites)	The number of sites was changed as follows: ***Previously read:*** "2-3, US Only" ***Now reads:*** "Up to 4, US Only"	Revised to expand recruitment.
2.2.1 (Table 1), 5.4.1	Content revised to emphasize that subjects who have an SBP < 90 mmHg, confirmed by repeat measurement, before the start of HD will be withdrawn/discontinued from the study.	Clarification that repeat measurement of SBP < 90 mmHg is required for confirmatory purposes.
5.1	***Previously read:*** • "4. Absence of residual renal function (i.e., no urine output)."	Clarification of renal function required for inclusion in the study.

	***Now reads**:* • "4. Absence of clinically-relevant residual renal function."	
	***Previously read**:* • "9. Must be on stable doses (> 4 weeks) of all treatments for concomitant diseases (e.g., diabetes, hypertension)." ***Now reads**:* • "9. Must be on stable doses (> 4 weeks) of all treatments for concomitant diseases (e.g., diabetes, hypertension), but this does not apply to medications for conditions related to ESRD (e.g., medications for calcium and phosphate control, anemia).	Clarification of treatments for concomitant diseases.
5.2	***Previously read**:* • "18. Concurrent or have recent participation in another interventional clinical trial. Prior clinical trial subjects must have discontinued investigational agents/devices at least 30 days prior to screening." ***Now reads**:* • "18. Concurrent or have recent participation in another interventional clinical trial. Prior clinical trial subjects must have discontinued investigational agents/devices at least 30 days prior to planned first use of the [redacted] column."	Clarification of timing of discontinuation of investigational agents/devices from prior clinical trials.
6.1.1	[redacted]	[redacted] address change.
7.1.1.2.2	The following content was added: "If screening and/or EOS occur on a day in which a subject is not receiving HD, vital signs will be measured after the subject has been seated/reclined for ~5 minutes."	Clarification of measurement of vital signs at screening and EOS.
7.3.1	Heading title was changed from "Screening" to "Screening/Run-In"	Revision of heading title for accuracy.
8.4.2.1	Content related to event reporting has been revised as follows: ***Previously read**:*	Revised to align with IRB reporting requirements.

	• "All SAEs (including SADEs and UADEs) must be reported to the IRB as soon as possible but in no event later than 10 working days after becoming aware of the event." ***Now reads:*** • "All applicable events (including UADEs) must be reported to the IRB as soon as possible but in no event later than 10 working days after becoming aware of the event."	
13.4	The following text was removed: "In compliance with The International Committee of Medical Journal Editors clinical trials registration policy and Section 801 of the FDA Amendments Act of 2007, this study will be registered by the Sponsor in ClinicalTrials.gov, a public trials registry which is sponsored by the National Library of Medicine. Notwithstanding the Sponsor's requirements for registration and data sharing in ClinicalTrials.gov,"	This content was removed as this Phase 1 study will not be published on ClinicalTrials.gov.
15.3	Testing of chloride was erroneously included at Visit 22; test was corrected to calcium (total).	Correction of laboratory testing at Visit 22.

Protocol Version 1.2 dated 06JAN2021
Replaces: Protocol Version 1.1 dated 21DEC2020

The following table describes changes from Version 1.1 (dated 21DEC2020) with justifications provided.

Section(s)	Description	Justification
Throughout	Protocol version update. ***Previously read:*** "V1.1_21DEC2020" ***Now reads:*** "V1.2_06JAN2021"	Version control.
5.2	***Previously read:*** • "8. […] Women of childbearing potential (WOCBP) must have a negative serum/urine pregnancy test at screening, prior to treatment, and at EOS." ***Now reads:*** • "8. […] Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and prior to treatment."	Clarification to reflect that only serum pregnancy tests will be conducted in WOCBP. In addition, because a negative serum pregnancy test is not required for eligibility at EOS (but is required for safety purposes), this requirement has been removed from Section 5.2 and added in Section 15.3.
7.1.1.1	Added that laboratory tests during run-in will include a pregnancy test for WOCBP.	Clarification to align with Exclusion Criterion #8

		which states that WOCBP must have a negative pregnancy test at screening and prior to start of the first treatment.
7.3.4	***Previously read**:* "In the event of early withdrawal or discontinuation of a subject who has been randomized and received at least 1 HD treatment, the EOS procedures will be performed […]" ***Now reads**:* "In the event of early withdrawal or discontinuation of a subject who has received at least 1 HD treatment with the [redacted] column, the EOS procedures will be performed […]"	Clarification to ensure alignment with Section 5.4.2. Handling of Participant Withdrawals/Discontinuation
15.3	Added serum pregnancy tests at V4 and EOS (WOCBP only) to the Schedule of Laboratory Assessments.	Clarification to align with Exclusion Criterion #8 which states that WOCBP must have a negative pregnancy test at screening, and prior to treatment. A negative pregnancy test at EOS is also required for safety purposes..

Protocol Version 1.1 dated 21DEC2020
Replaces: Protocol Version 1.0 dated 26OCT2020

The following table describes changes from Version 1.0 (dated 26OCT2020) with justifications provided.

Section(s)	Description	Justification
Throughout	Protocol version update. ***Previously read**:* "V1.0_26OCT2020" ***Now reads**:* "V1.1_21DEC2020"	Version control.
Throughout	Minor grammar, content, and style updates.	Minor content updates for clarity/accuracy/style of content.
Table of Contents and List of Abbreviations	Minor content updates.	Minor updates required to reflect revised content.
List of Definitions	The Definition for Intradialytic Hypotension/Hypotensive Event (IDH) has been revised as follows: ***Previously read**:* "A systolic blood pressure (SBP) < 90 mmHg that occurs during hemodialysis." ***Now reads**:* "A systolic blood pressure (SBP) < 90	Clarification that an IDH requires confirmation by repeat measurement.

	mmHg that occurs during hemodialysis and is confirmed by repeat measurement."	
Protocol Summary (Endpoints), 4.2.1	The Primary Endpoints have been revised as follows: ***Previously read**:* • "Safety and tolerability of each column size and each blood-flow rate. o Safety assessments will include the number of treatment-emergent adverse events (TEAEs), number of IDH events, and changes in total and free hemoglobin (Hgb). o Tolerability will be assessed by the proportion of subjects who can escalate to and tolerate each column size and blood-flow rate combination." ***Now reads**:* • "Safety and tolerability of each column size and each blood-flow rate. o Evaluation of safety and tolerability will include assessment of the rate and severity of all adverse events (AEs), with analysis of adverse device effects (ADEs), treatment-emergent AEs (TEAEs), number of IDH events, and changes in total and free hemoglobin (Hgb). o Tolerability will be assessed by the proportion of subjects who can escalate to and tolerate each column size and blood-flow rate combination."	Provision of additional detail and clarification of the specific safety and tolerability assessments that will be evaluated.
2.2.1	An additional mitigation strategy was added for IDH: "Withdrawal of subjects who have a systolic blood pressure (SBP) < 90 mmHg before the start of HD (confirmed by repeat measurement)."	Provision of additional precautionary safety measures to mitigate IDH.
	Additional potential risks (low incidence) and mitigation strategies were added for: allergic reaction/anaphylaxis, cramping, itching, headache, and hemolysis.	Provision of additional potential risks and mitigation strategies.
5.2	The previous Exclusion Criterion #4 was split and revised as follows (split also required renumbering of subsequent Exclusion Criteria): ***Previously read**:* • "4. History of hypersensitivity to heparin, the [redacted] column, or materials in the column." ***Now reads**:* • "4. History of hypersensitivity to heparin,	Provision of additional detail and clarification of exclusions related to hypersensitivity to heparin and/or the [redacted] column or its components.

	including heparin-induced thrombocytopenia." • 5. History of hypersensitivity to the [redacted] column or its components."	
5.4.1	In bullet #1, the following content was added: ***Previously read**:* • "Occurrence of an AE, that represents and unacceptable risk…" ***Now reads**:* • "Occurrence of an AE, including significant hemodynamic compromise, that represents an unacceptable risk…"	Clarification that significant hemodynamic compromise may require discontinuation from the study based on the determination of the investigator, Sponsor, or medical monitor.
	The content in Bullet #7 was expanded and an additional bullet was added: ***Previously read**:* • "A subject will be discontinued according to the discontinuation rules provided in Appendix 17.1." ***Now reads:*** • "A subject will be discontinued if they have a confirmed SBP < 90 mmHg before the start of an HD session. • A subject will be discontinued if the number of IDH events (defined as an SBP < 90 mmHg) during a treatment period exceeds the predetermined threshold of the subject's Historical IDH Rate after de-escalation to the lowest column size (see Appendix 17.1)."	Clarification that a subject will be discontinued due to a confirmed SBP < 90 mmHg prior to an HD session and/or IDH events in excess of the subject's Historical IDH Rate after de-escalation to the lowest column size.
8.1.1	The section heading was revised as follows: ***Previously read**:* • "Definition of Adverse Event and Adverse Device Effect" ***Now reads**:* • "Definition of Adverse Event, Procedure-Related Adverse Event, and Adverse Device Effect" The following text was also added to define a procedure-related adverse event: "In relation to Note 2 above, a sub-classification of an AE is a procedure-related AE (PRAE). A PRAE is an AE that most likely occurs as a result of HD or related procedures, irrespective of the investigational medical device. Examples of a PRAE in HD include vascular access site complications, including access hemorrhage and venous needle dislodgement; disruption or contamination of the	Revised to define a PRAE, with examples, to promote investigator awareness and understanding.

	dialysis water system; venous air embolism; sepsis; cardiac complications including arrhythmia, angina, and cardiac arrest; electrolyte imbalances including hypokalemia and hyperkalemia, etc. In cases where relatedness is unclear, a conservative stance is to consider the event as related to the investigational medical device."	
8.3	Section content expanded as follows: ***Previously read:*** • "At every clinic visit, subjects will be assessed for AEs and SAEs. After the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking a non-leading question such as the following: 1. "How are you feeling?" 2. "Have you had any changes since your last assessment/visit?" 3. "Have you taken any new medicines since your last assessment/visit?" ***Now reads:*** • "At very clinic visit, subjects will be assessed for AEs and SAEs. All AEs and SAEs will be monitored and recorded by trained and knowledgeable personnel to protect subjects from harm. At the beginning of each visit, after the subject has had an opportunity to spontaneously mention any problems that may have occurred during the preceding interdialytic interval, the investigator should inquire about any possible interdialytic AEs by asking a non-leading question such as the following: 1. "How are you feeling?" 2. "Have you had any changes since your last assessment/visit?" 3. "Have you taken any new medicines since your last assessment/visit?" During and for a period after each HD session, participating subjects will be closely monitored by qualified healthcare personnel who are trained in HD and who have experience in the types of AEs that typically occur during HD. Any events that occur during or after HD (before the subject leaves the clinic), will be assessed by the HD	Clarification of safety assessments and monitoring related to both procedures and personnel.

	personnel (e.g. hemodialysis technician or nurse) and discussed as appropriate with the investigator or designee."	
8.4.3	Section heading included in error.	Section heading removed to correct error.
15.2	The Kt/V assessment was removed from Visit 23 (EOS).	Assessment of Kt/V is not necessary as HD is not included in Visit 23 (EOS).
15.3	Expanded note to indicate that plasma-free Hgb should also be taken AFTER HD V4-V21.	Clarification of timing of laboratory measurement.
17.1	The content in the initial paragraph was updated and expanded as follows: ***Previously read:*** • "The purpose of the escalation rules is to ensure the safety of the subject when transitioning to a larger-size column, since the main risk of [redacted] – IDH – is related to column size." ***Now reads:*** • "The purpose of the escalation rules is to ensure the safety of the subject when transitioning to a larger-size column. Since the main risk of [redacted] – IDH – is related to column size, the occurrence of IDH will be the main criterion used to determine the appropriateness of escalation to a larger column size; however, other factors will be considered when escalating, including the overall status of the subject, other AEs, laboratory abnormalities, adequacy of HD, etc."	Clarification of the purpose of the escalation rules and definition of IDH.
	The initial bullet page was also updated as follows ***Previously read:*** • ***"Intradialytic hypotension/hypotensive (IDH) event:*** An SBP < 90 mmHg. ***Now reads:*** • ***"Intradialytic hypotension/hypotensive (IDH) event:*** An SBP < 90 mmHg confirmed by repeat measurement."	

17.1.1	The content in the initial paragraph was updated and expanded as follows: ***Previously read:*** • "A subject may be escalated to the next larger column size or next blood-flow rate if they experience no more than the number of IDH events described in Table 3, have a level ≥ 9 g/dL, and have no other safety signals that the investigator believes could put the subject at risk." ***Now reads:*** • "A subject may be escalated to the next larger column size or next blood-flow rate if they experience no more than the number of IDH events described in Table 3, maintain an Hgb level ≥ 9 g/dL, and have no other safety signals that the investigator believes could put the subject at risk. If a subject has an SBP < 90 mmHg (confirmed by repeat measurement) *before* the start of HD, the subject will be withdrawn from the study because this constitutes significant hemodynamic compromise."	Clarification of escalation rules with additional details related to SBP parameters.