EPIZON PHARMA, INC.

CLINICAL STUDY PROTOCOL

A Phase 1, Prospective Safety Trial of EPN-701 in Subjects with Stable End Stage Renal Disease (ESRD) Receiving Outpatient Hemodialysis

Protocol Number: EPN-701-001

IND Number: 129344

Amendment 3, Dated January 16, 2020

Replaces Protocol Version: Amendment 2, Dated: March 23, 2019

Sponsor: Epizon Pharma, Inc.
445 Park Avenue, Suite 908
New York, NY 10022
Telephone: +917.912.9900
Facsimile: +212.829.5611

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1. SPONSOR SIGNATORIES

SPONSOR:

John M. Rudey, Chairman
Epizon Pharma, Inc.
445 Park Avenue, Suite 908
New York, NY 10022, USA
Telephone: +1.917.912.9900
Email:Jrudey@epizonpharma.com

John M. Rudey
Signature

21 JAN 2020
Date

William E. Gannon Jr., MD
Chief Operating Officer
Epizon Pharma, Inc.
445 Park Avenue, Suite 90B
New York, NY 10022, USA
Telephone: +1.50B.487.0830
E-mail: wgannon@epizonpharma.com

Signature

16 JAN 2020
Date

SPONSOR'S MEDICAL REPRESENTATIVE:

James A. Tumlin, MD
Founder and Director of Nephronet Clinical Trials Consortium
923 Preserve Bluff Drive
Atlanta, GA 30518, USA

Telephone: +1.770.490.9203
Email: jamestumllnmdnephronet @gmail.com

Signature

17 JAN 2020
Date

2. INVESTIGATOR AGREEMENT

TITLE:	A Phase 1, Prospective Safety Trial of EPN-701 in Subjects with Stable End Stage Renal Disease (ESRD) Receiving Outpatient Hemodialysis
PROTOCOL NUMBER:	EPN-701-001
VERSION NUMBER:	6.0 (Amendment 3)
VERSION DATE:	January 16, 2020
IND NUMBER:	129344
TEST PRODUCT:	EPN-701
SPONSOR:	Epizon Pharma, Inc.

I agree to conduct this clinical trial according to the protocol described herein, and to comply with its requirements, subject to ethical and safety considerations and guidelines. I also agree to conduct this study in compliance with Good Clinical Practice (GCP) standards as defined by the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) and any other institutional requirements.

I understand that the information in this protocol is confidential and should not be disclosed to others without written authorization from Epizon Pharma, Inc., except to the extent necessary to: (1) obtain informed consent from persons to whom the drug may be administered; and (2) inform those directly involved in the execution or the scientific/ethical review of the study.

I understand that failure to comply with the requirements of the protocol may lead to my participation as an Investigator for this study to be terminated.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local clinical research associate (CRA).

3. STUDY ADMINISTRATIVE STRUCTURE

RESPONSIBILITY	NAME & CONTACT DETAILS
Sponsor Medical Monitor / Study Medical Monitor	Katherine M. Smith, MD 5205 Indigo Moon Way Raleigh, NC 27613 Telephone: +1.919.264.5626 E-mail: ksmith@safeharborpv.com
Independent Medical Monitor	J. Bruce McClain, MD 11673 Garnet Road Lovettsville, VA 20180 Mobile: +1.202.236.6975 E-mail: drjblmcclain@aol.com
Safety Reporting and Pharmacovigilance Analysis	MedAssessment, Inc. 14 Calle Vista Del Sol San Clemente, CA 92673-6913 Telephone: +1.949.369.1931 Website: www.medassessment.com
Contract Research Organization (CRO)	NephroSynergy, LLC 575 Professional Drive, Suite 250 Lawrenceville, GA 30046 Telephone: +1.423.943.4265 Fax: +1.888.242.1406 Email: jwhitson@nephrosynergy.com
Central Laboratory (Safety Laboratory, Biomarker, and PK Assessments) **Biomarker Laboratories (PIVKA-II, dp-ucMGP, and T-50; Respectively)**	Covance Central Laboratory Services 8211 SciCor Drive Indianapolis, Indiana 46214 Telephone: +1.317.271.1200 Fax: +1.317.273.4030 Website: www.covance.com Ventana Medical Systems, Inc Pharma Services Laboratory 1910 East Innovation Park Drive Tucson, AZ 85755 Telephone: +1.520.273.8520 Email: noah.theiss@roche.com University of Liège – Dept. of Chemistry Bone & Cartilage Markers Laboratory Hospital Avenue B35

RESPONSIBILITY	NAME & CONTACT DETAILS
	Route 52, Porte 52 4000 Liège Belgium Telephone: +00.324.366.8817 Email: anne-catherine.bekaert@chuliege.be Calciscon AG Aarbergstrasse 5 2560 Nidau Switzerland Telephone: +41.32.530.8860 Email: swapna.karthik@calciscon.com
Study Drug Packaging, Labeling, and Distribution	Sherpa Clinical Packaging dba PCI Pharma Services 6166 Nancy Ridge Drive San Diego, CA 92121 Telephone: +1.858.223.0841 Website: SherpaClinical.com
Institutional Review Board	Copernicus Group IRB 5000 CentreGreen Way, Suite 200 Cary NC 27513 Telephone: +1.919.465.4310 Facsimile: +1.919.465.4311 Email: irb@cgirb.com Website: www.wcgclinical.com

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4. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
AVF	arteriovenous fistula
BGP	bone Gla protein
BUN	blood urea nitrogen
β-hCG	beta-human chorionic gonadotropin
CBC	complete blood count
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
cMGP	carboxylated Matrix Gla Protein
CMP	complete metabolic panel
C_{max}	maximum plasma concentration
CPP	calciprotein particles
CRA	clinical research associate
CRO	contract research organization
CUA	Calcific Uremic Arteriolopathy (calciphylaxis)
CVA	cerebrovascular accident
dba	doing business as
DNA	deoxyribonucleic acid
dp-cMGP	desphospho-carboxylated Matrix Gla Protein
dp-ucMGP	dephosphorylated and uncarboxylated Matrix Gla Protein
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EDC	electronic data capture
EFSA	European Food Safety Authority
EOS	End-of-Study (visit)
EOT	End-of-Treatment (visit)
ESRD	end-stage renal disease
FAO	Food and Agriculture Organization (of the United Nations)
FDA	Food and Drug Administration
FSI	first subject in
GCP	Good Clinical Practice

Abbreviation	Definition
GGCX	gamma glutamate carboxylase
Gla	gamma-carboxyglutamic acid
GLP	Good Laboratory Practice
HBeAg	hepatitis B “e” antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
hs-CRP	high-sensitivity C-Reactive Protein
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IND	Investigational New Drug application
INR	International Normalized Ratio
IOM	Institute of Medicine
IP	investigational product
IV	intravenous(ly)
KH2	vitamin K hydroquinone
Kt/V	measure of dialysis adequacy; K=dialyzer urea clearance, t=duration of the dialysis session, V=volume of urea distribution
LC/MS/MS	liquid chromatography tandem mass spectrometry
LDL	low-density lipoprotein
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MGP	Matrix Gla Protein
MK-4	menaquinone-4
MK-7	menaquinone-7
mRNA	messenger ribonucleic acid
NADP	nicotinamide adenine dinucleotide phosphate
NOAC	novel oral anticoagulants
NOAEL	no-observed-adverse-effect-level
LSLV	last subject last visit
PCR	polymerase chain reaction
PIVKA-II	Protein Induced in Vitamin K Absence/Antagonist-II (also known as descarboxyprothrombin or des-gamma-carboxy prothrombin [DCP])
PK	Pharmacokinetic(s)
PT	preferred term
PTT	partial thromboplastin time

Abbreviation	Definition
RBC	red blood cell
RNA	ribonucleic acid
ROS	reactive oxygen species
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SMF	Site Master File
SOC	System Organ Class
SRC	Safety Review Committee
TG	triglycerides
T-50	Time to Formation of Secondary Calciprotein Particles
TIA	transient ischemic attack
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
USA/US	United States of America
USP	United States Pharmacopeia
VKD	vitamin K-dependent
VKOR	vitamin K oxidoreductase
VKORC1	vitamin K epoxide reductase C1
VKORC1L1	vitamin K epoxide reductase C1-Like-1
VKR	vitamin K reductase
WBC	white blood cell
WHO	World Health Organization

5. PROTOCOL SYNOPSIS

Study Title	A Phase 1, Prospective Safety Trial of EPN-701 in Subjects with Stable End Stage Renal Disease (ESRD) Receiving Outpatient Hemodialysis
Study Number	EPN-701-001
Clinical Development Phase	Phase 1
Indication	End Stage Renal Disease (ESRD) on hemodialysis
Study Design	This is a Phase 1, prospective, open label study to evaluate the safety, tolerability, and pharmacokinetics (PK) of EPN-701, administered once daily for 14 days in subjects with ESRD on a stable hemodialysis regimen.
Study Objectives	Primary Objectives: • To determine the safety and tolerability of EPN-701 (administered for two weeks at a daily dose of 10 mg) in subjects with ESRD on stable hemodialysis. Secondary Objectives • To determine, in subjects with ESRD on stable hemodialysis, the plasma levels of the following biomarkers after two weeks of EPN-701 treatment relative to baseline: uncarboxylated MGP; uncarboxylated osteocalcin; Activated Protein C; and Protein Induced Vitamin K Absence-II (PIVKA-II). Exploratory Objectives: • To determine the pharmacokinetic profile of EPN-701 in subjects with ESRD on stable hemodialysis. • To determine, in subjects with ESRD on stable hemodialysis, the plasma levels of the following biomarkers after two weeks of EPN-701 treatment relative to baseline: osteoprotegerin, Fetuin A, high-sensitivity C-Reactive Protein (*hs*-CRP) and Time to Formation of Secondary Calciprotein Particles (T-50 Test), including CPP size.
Study Population	A total of 15 eligible subjects with ESRD on a stable maintenance dialysis regimen will be enrolled and treated with EPN-701.
Inclusion Criteria	Subjects must meet all inclusion criteria to be enrolled in the study: 1. Male or female ≥18 years of age

	2. Diagnosed with ESRD and treated with stable maintenance hemodialysis at least three times a week for at least three months prior to the first dose of study drug. Subjects may have missed (less than or equal to) 4 hemodialysis sessions within three months prior to enrollment, provided that the Principal Investigator deems them suitable for study participation. 3. Clinically stable medical condition, consistent with ESRD, as judged by the investigator based on the results of screening safety evaluations (physical examination, medical history, clinical laboratory tests, vital signs, and 12-lead electrocardiogram [ECG]) 4. Written informed consent 5. Able and willing to comply with the requirements of the study protocol 6. For females of child-bearing potential: o Negative serum pregnancy test; o Abstinence (refraining from heterosexual intercourse) or use of an acceptable contraception for at least 1 month prior to screening, and willingness to continue for at least 1 month after the last study drug administration. A woman is considered to be of childbearing potential if she is post-menarche, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus, or bilateral tubal ligation). Examples of acceptable contraceptive methods include: hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

Exclusion Criteria	Subjects meeting any of the following exclusion criteria will be excluded from the study: 1. Chronic kidney disease not requiring hemodialysis 2. Acute kidney injury treated with hemodialysis 3. Diagnosis of confirmed calciphylaxis 4. History of any solid organ transplant 5. History of malignancy within 2 years of study enrollment, except for adequately treated carcinoma *in situ* of the cervix and non-melanoma skin carcinoma 6. History of any major surgery (defined as a surgical procedure involving the cranium, chest, abdomen, or pelvic cavity, or other procedure performed under general anesthesia) within 1 month prior to the first dose of study drug. Subjects with a recent (within <1 month) revision and/or placement of arteriovenous fistula (AVF) will be allowed to participate. 7. History of a major cardiovascular event (such as cerebrovascular accident [CVA], transient ischemic attack [TIA], myocardial infarction, unstable angina) within 1 month prior to the first dose of study drug. 8. Any co-existing disease or condition that may compromise the safety of study participants and/or the integrity of the study, including, but not limited to: o Class C or Class D Cirrhosis of the liver o Known intestinal malabsorption o Inability to take oral medication 9. Life-expectancy <3 months 10. Known history or positive serology for Human Immunodeficiency Virus (HIV), positive serologies of E antigen or with polymerase chain reaction (PCR) positive titers for hepatitis B virus (HBV). Subjects with positive serologies for hepatitis C but with negative PCR for active virus will be allowed. 11. Severe infection requiring intravenous (IV) antibiotics within two weeks prior to the first dose of study drug. 12. Warfarin taken within two weeks prior to the first dose of study drug. Subcutaneous heparin, enoxaparin and novel oral anticoagulants (NOAC; such as apixaban) are permitted. 13. Treatment with an investigational drug within four weeks prior to the first dose of study drug.

	14. Pregnancy or lactation 15. Any other disease or condition which, in the judgment of the Investigator, would place a subject at undue risk by being enrolled in the trial, or cause inability to comply with the trial.
Study Assessments & Schedule	A total of 15 consenting subjects meeting the study eligibility criteria will be enrolled and treated with EPN-701 10 mg (one 10 mg capsule to be taken orally once a day, at the same time each morning), for 14 days. The expected duration of study participation for an individual subject is approximately five weeks, including up to one week for screening, two weeks of study treatment, and two weeks of post-treatment safety follow-up. Subjects will undergo a total of 14 visits during their study participation: Screening visit (within seven days prior to the first dose of study drug), three visits per week during the two-week treatment, and two-week safety follow-up periods (coinciding with the subject's hemodialysis schedule), and the End-of-Study (EOS)/Early Termination visit. Baseline assessments will be completed prior to the first study drug intake on Day 1. End-of-Treatment (EOT) assessments will be completed after the last dose of study drug on study Day 15 (or earlier in case of an early discontinuation of the study treatment). The EOS/Early Termination visit will occur two weeks after the last dose of study drug (on study Day 29). Subjects will be monitored for adverse events (AEs), and concomitant medications will be recorded throughout their study participation (from screening through the EOS/Early Termination Visit). Additional safety assessments will include: physical examinations, safety laboratory tests (hematology, including complete blood count [CBC]; complete metabolic panel [CMP, including electrolytes, renal and liver function tests, and lipid profile]; and coagulation panel), vital signs measurements, and 12-lead ECG. In addition, occurrence of dialyzer clotting will be assessed at each dialysis session, and Kt/V (a measure of dialysis adequacy) will be calculated at baseline (as the average of the last three pre-study Kt/V values obtained as part of the subject's standard of care) and at the end of treatment. Blood for PK assessments will be sampled as follows: • On Day 1 (baseline) and Day 8 (Week 2, on-treatment): pre-dialysis (at the time of needle placement, denoted as 0 hours), immediately followed by study drug administration, and then at 1 hour (+/- 5 minutes), 2 hours (+/- 5 minutes), 3 hours (+/- 5

	minutes), 4 hours (+/- 30 minutes)/before needle removal, 6 hours (+/- 30 minutes), 8 hours (+/- 30 minutes), and 24 hours (+/- 60 minutes) after study drug administration; • On Days 3, 5, 10, 12, and 15: pre-dialysis (at the time of needle placement, at 0 hours), immediately followed by study drug administration, and then at 4 hours (+/- 30 minutes)/before needle removal; and • On Day 17 (Week 3, off-treatment) pre-dialysis only (at the time of needle placement). Pre- and post-dialysis blood samples for biomarker analyses will be collected at Baseline, and on select Mondays during the two-week treatment, and two-week safety follow-up periods. Refer to **Table 1**, Schedule of Study Activities for further details.
Investigational Medicinal Product (IMP; Test Product) identity, dose, and mode of administration	EPN-701 (a new formulation containing highly purified Menaquinone-7 or MK-7 as the active ingredient) is the test product in this study, and will be provided by the study sponsor at the following dosage strength: • 10 mg soft-gel capsule for oral administration. Each subject will take one 10 mg capsule of EPN-701 per day orally over 14 days. The study drug is to be taken at the same time each morning.
Comparator product identity, dose, and mode of administration	Not applicable; this is an uncontrolled study.
Efficacy Endpoints	Not applicable
Safety Endpoints	<u>Primary Safety Endpoint:</u> • Frequency of treatment-emergent AEs and treatment-emergent AEs assessed as related to the study drug (defined as possibly, probably, and definitely related events). A treatment-emergent AE is defined as any AE with an onset between the first dose of the study drug and the last study visit, or any AE with an onset prior to first dose that increases in severity or frequency after the first dose of study drug. Adverse events include both clinical events and laboratory abnormalities that are assessed as clinically significant. <u>Secondary Safety Endpoints:</u> • Frequency of serious adverse events (SAEs), AEs leading to study drug discontinuation, and AEs of special interest (AESI)

	• Changes from baseline in safety laboratory parameters • Changes from baseline in vital signs measurements • Changes from baseline in ECG parameters.
Biomarker Endpoints	Secondary Endpoints: • Plasma levels of the following biomarkers on Day 15 (end-of-treatment) and Day 22 compared to baseline: uncarboxylated MGP; uncarboxylated osteocalcin; Activated Protein C, and PIVKA-II protein. Exploratory Endpoints: • Plasma levels of the following biomarkers on Day 15 (end-of-treatment) and Day 22 compared to baseline: osteoprotegerin, Fetuin A, *hs*-CRP. • Time to Formation of Secondary Calciprotein Particles (T-50 Test), including CPP size.
Pharmacokinetic Endpoints	Exploratory Endpoints: • EPN-701 plasma concentrations (ng/mL) at each measured time-point will be determined according to standard procedures, using a validated high-performance liquid chromatography (HPLC) tandem mass spectrometric (LC/MS/MS) method. In addition, depending on the observed plasma levels, the following PK parameters may be determined for EPN-701: • Maximum plasma concentration (C_{max}) [ng/mL] • Time to maximum plasma concentration (T_{max}) [hr] • Area under the concentration-time curve (AUC) from time 0 to 24 hours (AUC_{0-24} [hr×ng/mL])
Interim Safety Assessments by the Safety Review Committee (SRC)	A SRC will review the safety data accumulated during the study at regular intervals. The SRC will be comprised of the Sponsor's Medical Monitor, Independent Medical Monitor, and the Principal Investigator. Further details will be provided in the SRC Charter.
Statistical Methods	Sample Size Calculation No formal sample size calculation was performed. The selected sample size of 15 subjects is consistent with preliminary safety and PK studies of a similar design and is expected to provide sufficient information to identify safety issues, while limiting subject exposure.

	Analysis Populations • The safety population will include all subjects who received at least one dose of study drug. • The PK population will include all subjects who received at least one dose of study drug and have sufficient plasma concentrations data for PK analysis. General Considerations • All analyses will be descriptive. Binary and categorical data will be summarized by number and percentage of subjects. Continuous data will be summarized by means, standard deviations (SDs), medians, and ranges (minimum, maximum), as appropriate. • All data will be included in appropriate per-subject listings. Efficacy Analyses Not applicable. Safety Analyses • Adverse Events: All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be included in per-subject listings. In addition, treatment-emergent AEs will be summarized in frequency tables, by MedDRA System Organ Class (SOC) and by Preferred Term (PT). Adverse events assessed as related to the study drug will be summarized in a similar manner. A summary of AEs by maximum severity grade will also be provided. • Concomitant Medications: All concomitant medications will be coded using the most current version of the World Health Organization (WHO) Drug Dictionary and will be included in per-subject listings. • Laboratory parameters will be summarized at each time point measured using descriptive statistics, including means, SDs, medians, and ranges, as appropriate. Change from baseline will be summarized similarly, with 95% confidence intervals (CIs) for each change. Shift tables may also be provided, if warranted by the data. All safety laboratory data will be included in appropriate per-subject listings, along with reference ranges, and indication of clinically significant departures from the respective reference ranges.

	• ECG parameters: will be included in appropriate per-subject listings and summaries. Pharmacokinetic Analyses EPN-701 plasma concentration data will be measured at specific timepoints (see **Table 1**), tabulated and summarized. Descriptive statistics for plasma concentrations and PK parameters will include arithmetic means and SDs, geometric means and coefficients of variation, medians, and ranges, as appropriate. Biomarker Analyses Biomarkers will be summarized in a similar manner as described for safety laboratory parameters, with summary at each time point along with change from baseline. Depending of the distribution of the biomarkers, transformations to minimize skew and outliers may be performed. Interim Analyses Not applicable.
Study Duration	Overall Study Duration: All subjects are expected to be enrolled within approximately three months. The end of the study is defined as the last subject last visit (LSLV), which is expected approximately six to seven months after the enrollment of the first subject. The actual length of the study and the time for final analysis will depend on the recruitment rate. Duration of Study Participation Per Subject: The expected duration of the study for an individual subject is approximately five weeks, including up to one week for screening, two weeks of study treatment, and two weeks of post-treatment safety follow-up. Subjects will undergo a total of 14 visits during the study participation.
Participating Centers	The study will be conducted at one to three dialysis centers in the United States.

The schedule of study activities is provided in **Table 1** below.

Table 1 Schedule of Study Activities

	WEEK -1	WEEK 1 ON-TREATMENT			WEEK 2 ON-TREATMENT			WEEK 3 POST-TREATMENT			WEEK 4 POST-TREATMENT			EOS/ EARLY TERMINATION
VISIT SCHEDULE	**Screening**	**1 BL**	**2**	**3**	**4**	**5**	**6**	**7 EOT**	**8**	**9**	**10**	**11**	**12**	
Study Day	**-7 to -1**	**1**	**3**	**5**	**8**	**10**	**12**	**15**	**17**	**19**	**22**	**24**	**26**	**29**
Day of the week		**Mon**	**Wed**	**Fri**	**Mon**	**Wed**	**Fri**	**Mon**	**Wed**	**Fri**	**Mon**	**Wed**	**Fri**	**Mon**
Informed Consent & HIPAA Authorization	X													
Demographics [1]	X													
Medical History [2]	X													
Disease History [3]	X													
Physical examination [4]	X							(X)						X
Weight and height measurements [5]	X	X	X	X	X	X	X	X						X
Standard 12-lead ECG [6]	X							X						X
Vital signs measurements [7]	X	X	X	X	X	X	X	X						X
Hematology, CMP, Coagulation panel [8]	X	X			X			X			X			X
Testing for HIV, Hepatitis B and C [9]	X													
Serum β-hCG Pregnancy Test [10]	X													
Eligibility Criteria	X	X												
Concomitant Medications [11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event recording [12]		X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration [13]		Once daily, from Day 1 through Day 14												
EPN-701 PK assessments [14]		X	X	X	X	X	X	X	X					
Kt/V assessment [15]		X						X						
Biomarker assessments														
MGP, Osteocalcin, Activated Protein C, PIVKA-II protein, Fetuin A, osteoprotegerin, hs-CRP, and Time to Formation of Secondary Calciprotein		X						X			X			

	WEEK -1	WEEK 1 ON-TREATMENT			WEEK 2 ON-TREATMENT			WEEK 3 POST-TREATMENT			WEEK 4 POST-TREATMENT			EOS/ EARLY TERMINATION
VISIT SCHEDULE	**Screening**	**1 BL**	**2**	**3**	**4**	**5**	**6**	**7 EOT**	**8**	**9**	**10**	**11**	**12**	
Study Day	**-7 to -1**	**1**	**3**	**5**	**8**	**10**	**12**	**15**	**17**	**19**	**22**	**24**	**26**	**29**
Day of the week		**Mon**	**Wed**	**Fri**	**Mon**	**Wed**	**Fri**	**Mon**	**Wed**	**Fri**	**Mon**	**Wed**	**Fri**	**Mon**
Particles (T-50 Test), including CPP size [16]														

Abbreviations: AE=adverse event; AESI=adverse event of special interest; ALT=alanine amino transferase; AST=aspartate amino transferase; BL=Baseline (visit); BUN=blood urea nitrogen; CMP=Complete Metabolic Panel; CPP=calciprotein particles; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End-of-Study (visit); EOT=End-of-Treatment (visit); β-hCG=beta-human chorionic gonadotropin (pregnancy test); HDL=high-density lipoprotein; *hs*-CRP=high sensitivity C-reactive protein; INR=international normalized ratio; K=dialyzer clearance; LC/MS/MS=liquid chromatography tandem mass spectrometry; LDL=low-density lipoprotein; MGP=Matrix Gla protein; PK=pharmacokinetic(s); PTT=partial thromboplastin time; RBC=red blood cell (count); RNA= ribonucleic acid; SAE=serious adverse event; t=time; T-50 Test=Time to Formation of Secondary Calciprotein Particles; V=volume of urea distribution; WBC=white blood cell (count)

Note: Visit 1 will be the Baseline visit. End-of-Treatment (EOT) assessments will be completed after the last dose of study drug on study Day 15/Visit 7 (or earlier in case of an early discontinuation of the study treatment).

[1] Demographic data include age, sex, and self-reported race/ethnicity.

[2] General medical history includes clinically significant diseases (except those listed under “Disease history”), surgeries, reproductive status, and any conditions/symptoms present prior to the first dose of study drug.

[3] Disease history includes details on the underlying condition, including renal (ESRD) and dialysis history.

[4] A complete physical examination will be performed at screening and at the EOS visit on Day 29. A symptom-driven (abbreviated) physical examination may be performed at the EOT visit (Day 15), if the investigator deems it clinically indicated.

[5] Subjects will undergo body weight and height measurement at screening/baseline, and body weight measurements (as part of their standard care on dialysis days) within 60 minutes pre-dialysis and within 60 minutes post-dialysis on each dialysis day during the 2-week treatment period (Visits 1 through 6), at the EOT visit (Day 15), and EOS visit (Day 29).

[6] Standard 12-lead ECG recordings will be obtained within 60 minutes pre-dialysis at screening/baseline, at EOT (Day 15), and at EOS (Day 29). ECG recordings should be performed after the subject has been resting in a supine position for at least 5 minutes, and prior to other procedures scheduled at that same time (e.g., blood draws).

[7] Vital signs (including blood pressure, heart rate, respiratory rate, and oral body temperature) will be measured at screening, and (as part of their standard care on dialysis days) within 30 minutes pre-dialysis and within 30 minutes post-dialysis at each treatment visit (Visits 1 through 6), at EOT (Day 15), and EOS (Day 29).

[8] All blood sampling will occur pre-dialysis (at the time of needle placement). Hematology panel includes: RBC count, hemoglobin, hematocrit, and WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), if clinically indicated. CMP includes: glucose, albumin, total protein, electrolytes (sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphate), renal function tests (BUN, creatinine), liver function tests (ALT, AST, bilirubin), and lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides). Coagulation panel includes: PTT, INR, and platelet count.

[9] Serology for: HIV, HBV (hepatitis B “e” antigen [HBeAg] and PCR for the active virus [HBV DNA]); and HCV (HCV antibody and PCR for active virus [HCV RNA])

[10] Women of child bearing potential must undergo a serum β-hCG pregnancy test within 7 days prior to the first dose of study drug, and the result must be negative for enrollment.

[11] All medications (including over-the-counter medications) or therapy administered to the subject during the 30 days prior to the first dose of study drug will be recorded at screening/baseline. Any changes to concomitant medications will be documented regularly throughout the study.

[12] All AEs with an onset between the time the informed consent is signed and 14 days after the last dose of study drug (EOS/Early Termination visit) are to be recorded on the appropriate Adverse Event CRF pages and in source documents. SAEs, AESIs, and pregnancies occurring during or within 30 days after the last dose of EPN-701 will also be reported in an expedited fashion. SAEs and AESI considered to be related to the study drug by the investigator, will be reported to the Sponsor even if they occurred after the protocol-specified reporting period (i.e., more than 30 days after the last dose of EPN-701). Any occurrence of dialyzer clotting (assessed at each dialysis session) is to be recorded as an AE.

[13] EPN-701 10 mg per day (1 capsule of 10 mg). The study drug will be taken at approximately the same time each morning. On hemodialysis days (Days 1, 3, 5, 8, 10, and 12), subjects will take their study drug dose pre-dialysis (immediately after needle placement and biomarker sampling, as applicable); on the remaining days during Weeks 1 and 2, subjects will take their study drug dose at home.

[14] Blood for PK assessments will be sampled as follows:

- On Day 1 (baseline) and Day 8 (Week 2, on-treatment): pre-dialysis (at the time of needle placement, denoted as 0 hours), immediately followed by study drug administration, and then at 1 hour (+/- 5 minutes), 2 hours (+/- 5 minutes), 3 hours (+/- 5 minutes), 4 hours (+/- 30

minutes)/before needle removal, 6 hours (+/- 30 minutes), 8 hours (+/- 30 minutes), and 24 hours (+/- 60 minutes) after study drug administration;

- On Days 3, 5, 10, 12, and 15: pre-dialysis (at the time of needle placement, at 0 hours), immediately followed by study drug administration, and then at 4 hours (+/- 30 minutes)/before needle removal; and
- On Day 17 (Week 3, off-treatment): pre-dialysis only (at the time of needle placement).

Plasma levels of EPN-701 will be determined using a validated high-performance LC/MS/MS method.

[15] Kt/V (a standard measure of dialysis adequacy) will be calculated at baseline (as the average of the last three pre-study Kt/V values obtained as part of the subject's standard of care), and at EOT (Day 15). In case the Kt/V value obtained at EOT is reduced compared to baseline (pre-study measurements), the Investigator will determine (in consultation with the Medical Monitor, as needed) if the event qualifies for reporting as an AE.

[16] Blood sampling will always occur pre-dialysis (at the time of needle placement): on Day 1 (Baseline), Day 15 (EOT), and Day 22 (1 week after the last study drug dose), for a total of 3 samples collected. Plasma levels of the following biomarkers will be assessed: uncarboxylated MGP; uncarboxylated osteocalcin, Activated Protein C, PIVKA-II protein, Fetuin A, osteoprotegerin, *hs*-CRP, and Time to Formation of Secondary Calciprotein Particles (T-50 Test), including CPP size. Instructions for specimen collection and handling will be included in the laboratory manual provided by the Central Laboratory.

6. BACKGROUND

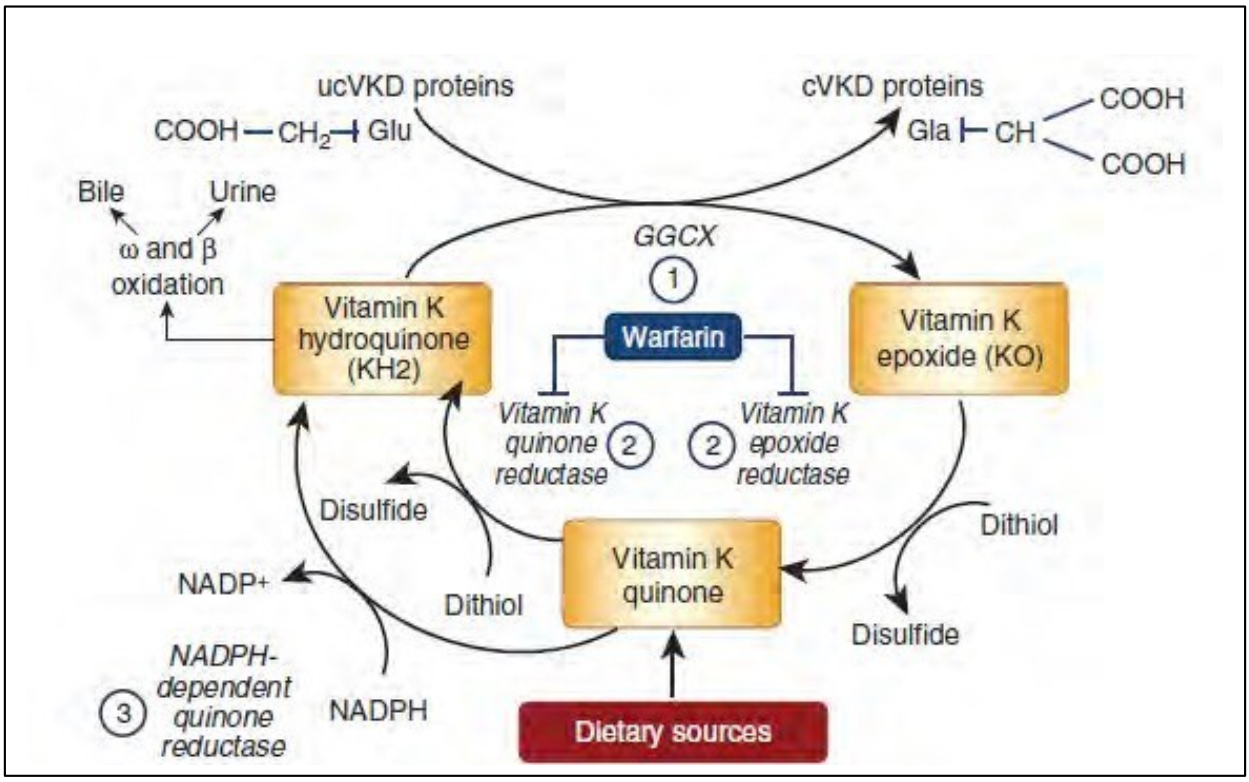
The current Phase 1 clinical trial is a prospective safety study of EPN-701 in subjects currently receiving stable hemodialysis for end-stage renal disease (ESRD). EPN-701 is a new formulation containing highly purified MK-7. MK-7 belongs to a family of compounds called menaquinones, collectively known as vitamin K2. EPN-701 is being developed for the treatment of calciphylaxis (also referred to as Calcific Uremic Arteriolopathy [CUA]), a rare, but potentially fatal complication of chronic kidney disease (CKD), predominantly affecting patients with ESRD on dialysis. The condition is characterized by calcification of subcutaneous arterioles and infarctions of the adjacent subcutis and skin (Janigan 2000; Brandenburg et al. 2016; Brandenburg et al. 2017). While the mechanisms for soft tissue calcification are not fully understood; there is a growing body of evidence that the uremic condition of both CKD and ESRD patients contributes to a functional deficiency of vitamin K. Subject to approval by the FDA, EPN-701 would be the first and only drug approved for the orphan indication calciphylaxis (CUA) to address peripheral soft tissue calcification and medial calcification of the smooth muscle cells of the vasculature. The following section provides an overview of (i) the impact of ESRD and hemodialysis on the vitamin K cycle; (ii) long-acting derivatives of vitamin K2; non-clinical and clinical background on EPN-701, and rationale for the current study, including key study design elements.

6.1 BACKGROUND ON VITAMIN K2

6.1.1 Vitamin K Metabolism and the Impact of Hemodialysis

Vitamin K is an essential enzymatic co-factor that is required for posttranslational modifications of vitamin K-dependent (VKD) proteins. Of the numerous VKD proteins, several are clinically relevant to ESRD patients. They include the central coagulation factors such as factors II, VII, IX, and X, as well as intercellular matrix proteins including matrix gamma-carboxyglutamic acid (Gla) protein (MGP) and osteocalcin (also referred to as bone Gla protein [BGP]). It has been proposed that vitamin K is reduced to vitamin K hydroquinone (KH2) via two pathways: a warfarin-sensitive pathway (by vitamin K epoxide reductase [VKORC1]) and a warfarin-resistant pathway (Tie and Stafford, 2016). It is only the reduced form of vitamin K that can function as a co-factor for gamma glutamate carboxylase (GGCX) which catalyzes the carboxylation of VKD proteins (Gallieni and Fusaro, 2014). Warfarin blocks the generation of vitamin K hydroquinone by acting as an inhibitor of the vitamin K recycling (**Figure 1**). The enzymatic carboxylation of glutamate residues results in further oxidation of vitamin KH2 to 2,3-epoxide Vitamin K. The final step of the vitamin K cycle requires the enzymatic reduction of vitamin K 2,3-epoxide back to its native structure. This step is catalyzed by VKORC1 and is a component of the vitamin K cycle along with warfarin (**Figure 1**) (Gallieni and Fusaro, 2014).

Figure 1 – Vitamin K Cycle



Conversion of glutamate (Glu) to g-carboxyglutamate (Gla) residues by g-glutamyl carboxylase (GGCX) (1) is essential for the activation of vitamin K-dependent (VKD) proteins. g-Carboxylation transforms undercarboxylated (ucVKD) into carboxylated (cVKD) proteins. Vitamin K hydroquinone (KH2) is oxidized to vitamin K epoxide (KO). KO is converted to vitamin K quinone by vitamin K epoxide reductase (2). A similar reductase enzymatic reaction (2) converts vitamin K quinone back into KH2. Another reductase, NAD(P)H-dependent vitamin K reductase (3), or DT-diaphorase, can also catalyze the same conversion into KH2. Warfarin inhibits the reductase activity (2) that is dithiol dependent but not the NADPH-dependent reductase (3), whose substrate can be dietary vitamin K.

Source: Gallieni and Fusaro, 2014

Recent studies have shown that VKOR has two distinct isoenzymes (VKORC1 and VKORC1-Like-1 [VKORC1L1]) that differ in both enzymatic properties and tissue distribution (Tie et al. 2011). VKORC1 and VKORC1L1 both catalyze the reduction of 2,3-epoxide vitamin K via vitamin K quinone to vitamin K hydroquinone. VKORC1 is the key enzyme of the classical vitamin K cycle by which VKD proteins are γ-carboxylated by the hepatic GGCX. In contrast, the VKORC1 paralog enzyme, VKORC1L1, is mainly responsible for antioxidative function by reduction of vitamin K to prevent damage by intracellular reactive oxygen species (ROS) (Caspers et al. 2015). The available data also suggest that there is an as-yet-unidentified vitamin K reductase (VKR) (different from VKORC1) in the vitamin K-dependent carboxylation that allows warfarin poisoning to be overcome (Tie and Stafford, 2016).

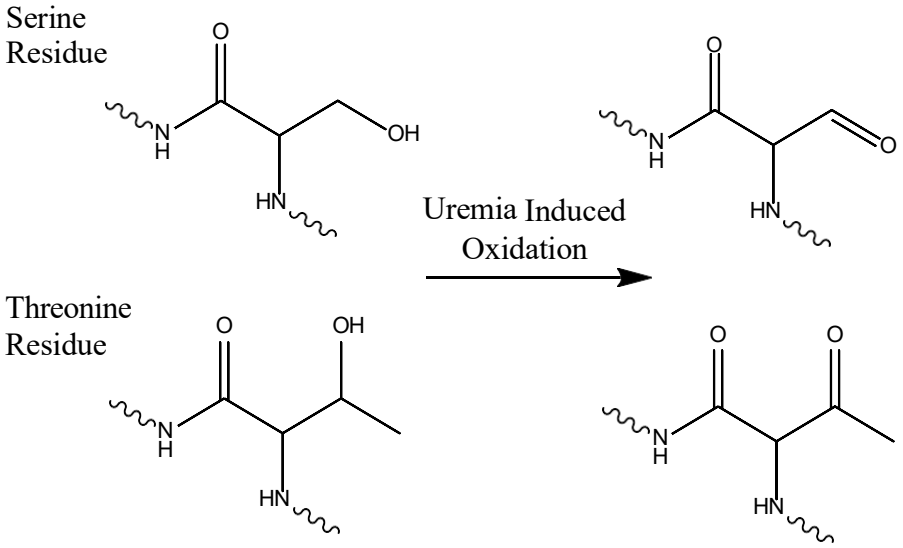
Westhofen *et al* have shown that compared to VKORC1, VKORC1L1 has a 3-fold lower affinity for 2,3-epoxide vitamin K (Westhofen et al. 2011). Subsequent work supported the hypothesis that VKORC1L1 is a specialized isoform that protects against oxidant injury through the regeneration of vitamin K. When cultured HEK293T cells were incubated with hydrogen peroxide

(H_2O_2), VKORC1L1 expression was increased and evidence of membrane oxidant injury was reduced (Westhofen et al. 2011; Tie et al. 2013). Cumulatively, observations reported to date suggest that any condition or procedure (i.e. hemodialysis) that blocks re-constitution of vitamin K predisposes that tissue to pathologic calcification (Caspers et al. 2015).

It is widely recognized that despite dietary deficiencies, vitamin K levels among ESRD patients may not be reduced. For example, *Holder et.al* studied 172 stable dialysis patients and found that only 6% of patients exhibited a clinically significant deficiency in vitamin K. However, when patients were examined for the level of uncarboxylated osteocalcin, 60% of patients had reduced levels (Holden et al. 2010). To confirm that this was a general effect of reduced vitamin K activity, the authors also measured PIVKA-II; another vitamin K-dependent protein. Indeed, 90% of both CKD and ESRD patients were found to have reduced levels of carboxylated prothrombin (Holden et al. 2010). In a similar study, Pilkey *et al* measured the vitamin K1 levels in 142 ESRD patients and found that most patients had adequate vitamin K stores but 93% of patients had uncarboxylated osteocalcin levels that were greater than 20% of the total osteocalcin levels, consistent with a subclinical vitamin K deficiency (Pilkey et al. 2007). It is interesting to note that there was no correlation between total vitamin K1 and the levels of circulating of uncarboxylated osteocalcin. This unexpected finding is consistent with the hypothesis that in uremic patients, total vitamin K levels can be normal while generation of reduced forms are blocked by the oxidative properties of uremia (Stockler-Pintoa et al. 2016).

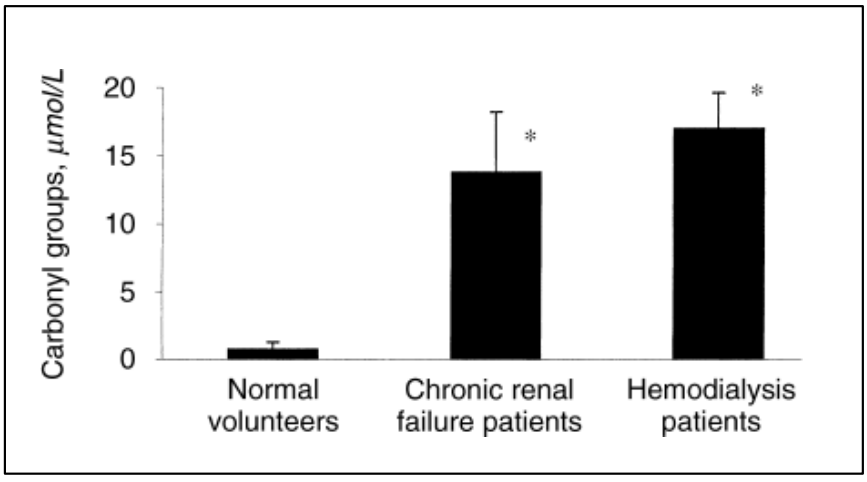
Evidence in the literature suggests that insufficient availability of menaquinones is associated with higher levels of dephosphorylated and uncarboxylated MGP (dp-ucMGP), and there is a significant correlation between dp-ucMGP and presence of soft tissue calcification (Schurgers et al., 2010; Delanaye et al. 2014). These observations suggest that some aspect of the uremic condition or even the process of dialysis neutralizes the carboxylating effects of vitamin K. Pioneering work by Himmelfarb et al. and others have confirmed that the simple delivery of hemodialysis can lead to the oxidation of numerous tissue proteins (Himmelfarb et al. 2000), such as the oxidation of the hydroxyl amino acid side chains to carbonyl groups (see **Figure 2**).

Figure 2 – The Oxidation of Protein Residues Serine and Threonine



In a study of CKD and ESRD patients, using carbonyl side chain oxidation as a measure of global oxidant burden, Himmelfarb *et al* demonstrated that both CKD and ESRD patients exhibit a higher percentage (15-fold) of carbonyl proteins compared to normal controls (see **Figure 3**). The percentage of carbonyl proteins was even higher among patients receiving dialysis, demonstrating that not only does dialysis not reduce oxidative burden, it appears to contribute to it (Himmelfarb et al. 2000). We propose that the oxidative load generated by the delivery of hemodialysis leads to oxidation of the functional KH2 to the non-functional native vitamin. The oxidation of KH2 by hemodialysis may block its ability to function as a co-factor for GGCX, which downstream leads to reduced gamma carboxylation of vitamin K-dependent proteins.

Figure 3 – *In vivo* Plasma Protein Carbonyl Formation



*P=0.05 vs. normal volunteers (N=10 in each group). Error bars represent standard error of the mean.

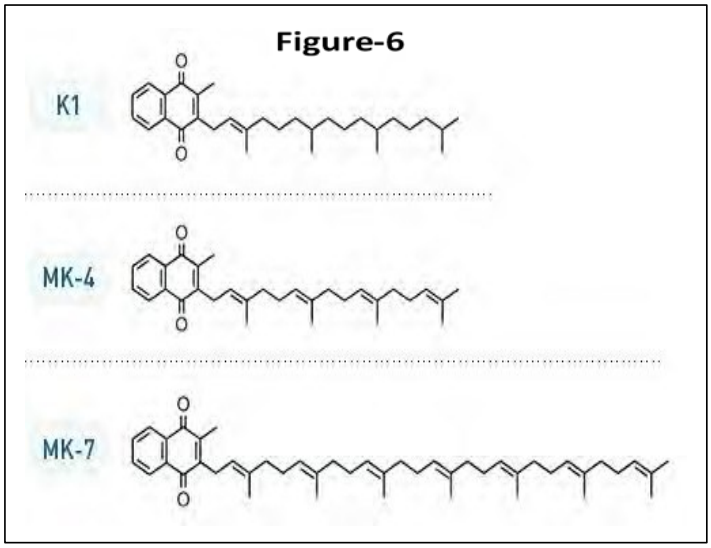
Source: Himmelfarb et al. 2000

6.1.2 Long-Active Derivatives of Vitamin K2: Therapeutic role for Menaquinone-7

EPN-701 is a new formulation containing highly purified menaquinone-7 (MK-7) that belongs to the vitamin K2 family of compounds. Subject to approval by the FDA, EPN-701 would be the first and only drug approved for the orphan indication Calciphylaxis (also referred to as Calcific Uremic Arteriolopathy [CUA]), specifically to address peripheral soft tissue calcification and related calcification of the medial smooth muscle cells of the vasculature present in most ESRD patients. Menaquinones have a common functional naphthoquinone ring system (also shared with phylloquinone) and an unsaturated polyisoprenyl side chain. They are designated based on the length of the aliphatic side chains attached to the naphthoquinone ring (Booth and Suttie, 1998; Shearer and Newman, 2008). Menaquinone nomenclature is based on the number of isoprenoid units, and ranges from 1 to 15 (e.g., MK-7 for the vitamer with a side chain consisting of 7 isoprenoid units) (Marles et al. 2017). The chemical structure of MK-4 and MK-7 compared to phylloquinone (vitamin K1) is presented in **Figure 4**. Although both phylloquinones and menaquinones are fat-soluble, their lipophilicity increases substantially at increasing chain length. Thus, when compared to MK-4, MK-7 has high lipid solubility, greater tissue concentration and longer plasma half-life. While MK-7 and MK-4 are both well absorbed in humans, the plasma levels of MK-7 are significantly higher due to its longer half-life of 72 hours. In contrast, MK-4 has a half-life of approximately 3 hours (Schurgers and Vermeer, 2002; Schurgers et al. 2007c).

Dietary sources of menaquinones include chicken, egg yolk, dairy products, cow liver, and fermented foods such as cheese, yogurt, sauerkraut, and natto, a traditional Japanese food made from soybeans fermented with *Bacillus subtilis varnatto* (Schurgers et al. 2007c; Marles et al. 2017).

Figure 4 – Vitamin K Structures



The naphthoquinone ring system shared by phylloquinones (vitamin K1) and menaquinones MK-4 and MK-7 (vitamin K2). The designation of MK-4 versus MK-7 is dependent upon the length of the aliphatic side chains attached to the naphthoquinone ring.

In addition, there are more than 200 dietary supplement products containing MK-7 currently on the market in the United States, the majority of which have a manufacturer's suggested MK-7 dose of 50 µg/d (NIH DSLD 2016). The Acceptable Daily Intake is 120 µg/day (FDA 2012).

6.2 BACKGROUND ON EPN-701

EPN-701 is a new formulation containing highly purified MK-7. MK-7 belongs to a family of compounds called menaquinones, collectively known as vitamin K2.

The following sections provide an overview of non-clinical and clinical data on MK-7. For further details, refer to the EPN-701 Investigator's Brochure.

6.2.1 Summary of Nonclinical Studies

The active ingredient in EPN-701 (MK-7) has been studied extensively in a variety of nonclinical animal models.

In a rat model of cardiovascular calcification, MK-7 supplementation inhibited the development of cardiovascular calcification and the inhibition was due to a direct effect on secondary mineralization of damaged vascular structures and not to a reduction in vascular damage. MK-7 supplementation also inhibited the increase in aortic alkaline phosphatase activity and resulted in a 10-fold increase in the expression of the MGP messenger ribonucleic acid (mRNA) in the aorta (Scheiber et al. 2015). Given that MGP is a potent inhibitor of arterial calcification, EPN-701 administration could be a beneficial treatment for calciphylaxis patients.

Published non-clinical toxicology studies of MK-7 include single-dose toxicity studies in mice and rats, and two-week, five-week, and two 13-week repeat-dose toxicity studies in rats. Administration of single oral doses of MK-7 at 2000 mg/kg (equivalent to a human dose of 9730 mg) to five female mice was not associated with signs of toxicity during the 14-day observation period (Pucaj et al. 2011). There were no signs of toxicity, effects on body weight (growth), or gross pathologic findings at necropsy after administration of 0.5, 1,10, 20, 2000 mg/kg/day (equivalent to human doses of 5, 10, 97, 194, 19400 mg/day, respectively) to eight rats (four male, four female) for 14 days (Ravishankar et al. 2015). In a Good Laboratory Practice (GLP)-compliant study with 13-week repeat dosing in rats, the no-observed-adverse-effect-level (NOAEL) was determined to be 10 mg/day, the highest dose tested (Pucaj et al. 2011), which is equivalent to a dose level of 97 mg/day in a 60-kg human subject. The five-week NOAEL for effects on cardiovascular function was also 10 mg/kg/day (97 mg/day in a 60-kg human subject), the only dose level tested (Siltari et al. 2014). These studies support the 10 mg/day dose in the EPN-701-001 clinical study as safe, given that there is a 10-fold safety margin from the NOAEL human equivalent dose.

Genotoxicity studies have shown that MK-7 has no mutagenic or clastogenic potential (Ravishankar et al. 2015).

Refer to the EPN-701 Investigator's Brochure for further details on the nonclinical studies.

6.2.2 Summary of Clinical Studies of EPN-701

The current EPN-701-001 study will be the first clinical investigation of EPN-701 in humans. Data on the clinical benefits and safety of MK-7 (the active ingredient in EPN-701) are available from numerous clinical trials and are briefly summarized below.

6.2.2.1 Summary of the Clinical Benefits of MK-7

The active ingredient in EPN-701 (MK-7) has been studied extensively in humans. Published reports of clinical trials conducted with MK-7 include studies evaluating dietary menaquinone intake, studies evaluating MK-7 as a nutritional supplement and clinical studies evaluating the effect of MK-7 on various disease indications.

High dietary menaquinone intake was associated with several beneficial effects in clinical trials involving more than 57,000 women and men, including: (1) Reduced coronary calcification in a cohort of 564 post-menopausal women (Beulens et al. 2009); (2) Reduced risk of coronary heart disease (CHD) in 16,057 women aged 49-70 years (Gast et al. 2008); (3) Reduced relative risk (RR) of CHD mortality, all-cause mortality and severe aortic calcification in 4807 subjects with no history of myocardial infarction at baseline (Geleijnse et al. 2004); (4) No increase in the risk of stroke (hemorrhagic, ischemic, or overall) in a prospective cohort of 35,476 Dutch men and women (average age of 49 years, 74% women) during a follow-up of approximately 12 years (Vissers et al. 2013); (5) In addition, results of one study involving 105 women suggested that higher MK-7 level resulting from natto consumption may contribute to the relatively lower fracture risk in Japanese women (Kaneki et al. 2001).

Long-term use of MK-7 supplements (180 µg/day for 3 years) improved arterial stiffness in 244 healthy postmenopausal women enrolled in a double-blind, randomized, placebo-controlled trial (Knapen et al. 2015).

In a prospective cohort analysis of 7216 participants at high cardiovascular disease risk, individuals who increased their intake of vitamin K1 or K2 during the follow-up period (median, 4.8 years) had a significantly lower risk of cancer and all-cause mortality, and no increase in cardiovascular mortality compared to those who decreased or did not change their intake (Juanola-Falgarona et al. 2010).

6.2.2.2 Summary of the Clinical Safety of MK-7

The safe use of MK-7 is supported by a body of published literature. Multiple studies have been performed in humans with MK-7 at various doses and frequencies, both in healthy volunteers and patients with various diseases. Several published clinical trials evaluated the safety of MK-7. Cumulatively, the findings from these studies indicate, that treatment with MK-7 at levels of up to 180 µg/day for 3 years (Knapen et al. 2013; Knapen et al. 2015), or up to 360 µg/day for 12 weeks (Theuwissen et al. 2012; Dalmeijer et al. 2012), or of up to 1080 µg three times weekly for 8 weeks (Caluwé et al. 2014) in treatment populations of up to 120 subjects was associated with no significant adverse effects compared with placebo. Adverse effects specifically attributed to MK-7 were limited to gastrointestinal upset associated with the product's smell (Marles et al. 2017).

Similarly, a systematic review and meta-analysis of 13 randomized controlled trials (N=1366) evaluating vitamin K1 and K2 supplementation for the prevention of bone fractures, none of the included studies reporting any serious adverse events (SAEs) associated with vitamin K (Cockayne et al. 2006).

A comprehensive review of the available evidence supporting the safety of MK-7 as an ingredient of dietary supplements was recently published (Marles et al. 2017). A search of the literature by the Institute of Medicine (IOM) revealed no evidence of toxicity associated with the natural menaquinones. Given the lack of adverse effects in humans or animals consuming high doses of vitamin K, the IOM was unable to derive a Tolerable Upper Intake Level (IOM 2001). The World Health Organization (WHO) and Food and Agriculture Organization (FAO) of the United Nations (WHO/FAO 2004) concluded that oral natural K vitamins seem to be free of toxic side effects, an observation based on clinical administration of doses of 10-20 mg/day or more. The European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies conducted a safety assessment of vitamin K2 (principally MK-7) added to food for nutritional purposes (EFSA 2008) and concluded there were no adverse effects of MK-7 on blood coagulation at doses of up to 6 µg/kg/day in adults and 1.5 µg/kg/day in children.

Overall, the conclusions of the reviews by all agencies have been supportive of a favorable benefit to risk ratio for vitamin K2 (Marles et al. 2017).

6.2.3 Clinical Pharmacokinetics of EPN-701

The current EPN-701-001 study will be the first investigation of the pharmacokinetics (PK) of EPN-701 in humans. Published clinical PK data for MK-7 is available in the literature.

In a study comparing the pharmacokinetic profile and the efficacy of MK-7 and vitamin K1, in healthy volunteers, maximum serum concentrations of MK-7 were seen approximately 4 hours after intake, followed by a steep decline in serum concentrations and then a second phase at 8-96 hours in which MK-7 remained stable for up to 4 days or more. MK-7 was shown to have a much longer half-life than vitamin K1 (68 hours vs 1-2 hours). Both MK-7 and vitamin K1 showed linear dose-response curves at 4 hours post treatment, from 0 to 500 µg; however, at 24 hours, MK-7 at 100 µg gave an upper limit of normal range for total serum vitamin K (1 µg/L), whereas there was no effect of vitamin K1 at up to 200 µg. MK-7 accumulated during the first two weeks until it reached a plateau level of approximately 6 µg/L (Schurgers et al. 2007c).

6.2.4 Anticipated Risks Associated with EPN-701

As detailed in Section 6.2.2.2, several published clinical trials evaluated the safety of MK-7. Cumulatively, the findings from these studies indicate, that treatment with MK-7 at individual daily doses of up to 1080 µg three times per week (Caluwé et al. 2014) was not associated with significant adverse effects compared with placebo. Adverse effects specifically attributed to MK-7 were limited to gastrointestinal upset associated with the product's smell (Marles et al. 2017).

There is a risk for interaction between EPN-701 and anticoagulant drugs (Marles et al. 2017).

Additional details are provided in the EPN-701 Investigator's Brochure.

6.2.5 Benefit-Risk Assessment

Based on the publicly available data demonstrating the clinical benefits and safety of MK-7 supplementation, EPN-701 is expected to have an acceptable safety profile in subjects with ESRD on hemodialysis, despite the higher dose to be evaluated in the current study (10 mg/day) compared to the daily doses administered in clinical trials of MK-7 supplementation (up to 1080 µg three times per week). Nevertheless, appropriate measures will be implemented to evaluate and minimize the potential risks related EPN-701 throughout the study. These will include continuous adverse event monitoring, and regular clinical and laboratory safety assessments. A Safety Review Committee (SRC) will review the safety data accumulated during the study at regular intervals. The SRC will be comprised of the Sponsor's Medical Monitor, Independent Medical Monitor, and the Principal Investigator. Further details will be provided in the SRC Charter.

6.3 RATIONALE FOR THE STUDY AND STUDY DESIGN

6.3.1 Rationale for the Study and Study Population

As detailed in Section 6.1, there is a growing body of evidence suggesting that both CKD and ESRD patients have a primary, functional deficiency of vitamin K as evidenced by reduced circulating levels of carboxylated forms of MGP and osteocalcin. Due to the loss of these proteins and their protective effects against soft tissue and vascular calcification, ESRD patients on hemodialysis are at risk of developing calciphylaxis.

Given the therapeutic potential of MK-7 in patients with ESRD on dialysis, the current clinical study is a Phase 1 prospective safety and PK study of EPN-701 in 15 subjects currently receiving stable hemodialysis for ESRD. Patients who have developed calciphylaxis will be excluded from the current study.

The primary objective of the EPN-701-001 study is to determine the safety and tolerability of EPN-701 (administered for two weeks at a daily dose of 10 mg) in subjects with ESRD on chronic stable hemodialysis.

Once the safety and tolerability of the 10 mg dose is determined in the current Phase 1 study, a Phase 2b clinical trial is planned to determine whether EPN-701 can normalize levels of calcium-chelating proteins and subsequently accelerate the rate of healing of calciphylaxis lesions.

6.3.2 Rationale for the EPN-701 Dose and Schedule

In a GLP-compliant study evaluating 13-week repeat dosing in rats, the NOAEL was determined to be 10 mg/kg/day, the highest dose tested (Pucaj et al. 2011), which is equivalent to a dose of approximately 97 mg/day in a 60-kg human subject. Additionally, a two-week repeat dose study in rats included dosing MK-7 as high as 2000 mg/kg/day and resulted in no signs of toxicity (Ravishankar et al. 2015). This equates to a human equivalent dose of approximately 19.4 g/day.

There is no known published LD-50 level for menaquinone-7.

The dose selected for the current clinical study is 10 mg/day, providing a 10-fold safety margin over the established NOAEL in rats. Therefore, the available data on MK-7 provide sufficient evidence of safety to support the proposed clinical study evaluating EPN-701 in humans.

In addition, the existing literature (Westenfeld et al. 2012; Caluwe et al. 2014) indicates that administration of 1.0 mg of MK-7 resulted in an approximately 50% absolute reduction/conversion of uncarboxylated matrix GLA protein to carboxylated matrix GLA protein, which is the only functional form of the protein capable of inhibiting the deposition of calcium in soft tissues. Therefore, a 10 mg dose of EPN-701 is anticipated to be sufficient to augment the carboxylation of MGP-1 to levels that will prevent additional calcification of the skin and soft tissues in patients with calciphylaxis.

6.3.3 Rationale for Biomarker Assessments

A significant proportion of ESRD patients on hemodialysis have functional, but modifiable, vitamin K deficiency (Cranenburg et al. 2012; Elliott et al. 2014), and multiple biomarkers have been tested as measures of vitamin K status in these patients (Elliott et al. 2014). PIVKA-II is a measure of prothrombin undercarboxylation, with elevated levels corresponding to poorer vitamin K status. As a biomarker of vitamin K status, PIVKA-II has the advantage of being independent of kidney function and lipid profile (Elliott et al. 2014).

MGP is a potent calcification inhibitor of the arterial wall and other soft tissues, and its activity depends on vitamin K-dependent γ-glutamate carboxylation (Schurgers et al. 2007a; Westenfeld et al. 2012; Schurgers et al. 2013; Marles et al. 2017). Uncarboxylated MGP, formed as a result of vitamin K deficiency, is associated with cardiovascular disease. Recent studies suggest poor vitamin K status in hemodialysis patients (Westenfeld et al. 2012). The circulating inactive form of MGP (dp-ucMGP) was shown to increase progressively in patients with CKD (Schurgers et al. 2010) and to be predictive of vitamin K status and correlated with vascular calcification in patients on hemodialysis (Delanaye et al. 2014). Plasma dp-ucMGP has therefore been proposed as a surrogate marker for vascular calcification in CKD (Schurgers et al. 2010). In addition, lower levels of circulating desphospho-carboxylated MGP (dp-cMGP) was proposed as a predictor of mortality in dialysis patients (Schlieper et al. 2011).

Osteocalcin is a non-collagenous bone matrix protein synthesized by mature osteoblasts, and involved in bone formation and regulation of bone mineralization (Elliott et al. 2014; Marles et al. 2017). The proportion of osteocalcin that is uncarboxylated is a sensitive marker of vitamin K status in bone, and subclinical vitamin K deficiency is defined by an increase in the proportion of uncarboxylated osteocalcin above 20% (Elliott et al. 2014). Supplementation with MK-7 at doses of 100–200 mg/d for 4 to 12 weeks was shown to increase the ratio of carboxylated to undercarboxylated osteocalcin significantly and in a dose-dependent manner (Inaba et al. 2015).

Vitamin K-dependent γ-carboxyglutamate proteins are synthesized in the liver, and help maintain normal blood coagulation through a balance of both procoagulant factors (II, VII, IX, and X) and anticoagulant proteins (C and S) (Schurgers et al. 2007c; Marles et al. 2017). Activated Protein C regulates the coagulation process by neutralizing the procoagulant activities of factors V and VIII in the presence of the cofactor Protein S (Marlar and Gausman, 2017). Hypercoagulable

states, such as protein C and/or protein S deficiencies have been reported in patients with calciphylaxis (the ultimate target population for EPN-701), and proposed as factors increasing the likelihood of calciphylaxis development (Wilmer and Magro, 2002; Nigwekar et al. 2008).

In a randomized study evaluating the effect of vitamin K2 supplementation on functional vitamin K deficiency in adult hemodialysis patients, patients on hemodialysis (N=53) had 4.5-fold higher dp-ucMGP and 8.4-fold higher uncarboxylated osteocalcin levels compared with healthy age-matched controls (N=50). PIVKA-II levels were elevated in 49 hemodialysis patients. Vitamin K2 supplementation induced a dose- and time-dependent decrease in circulating dp-ucMGP, uncarboxylated osteocalcin, and PIVKA-II levels. Response rates in the reduction in dp-ucMGP levels were 77% and 93% in the groups receiving 135 µg and 360 µg of menaquinone-7, respectively (Westenfeld et al. 2012). The results of this study provide a rationale for the use of plasma PIVKA-II, MGP, and osteocalcin as biomarkers in an interventional clinical trial of vitamin K supplementation in hemodialysis patients.

Fetuin A has been characterized as a critical regulator of calcification in humans, and as such is of interest to monitor in interventions targeting calcification (Jahnen-Dechent et al., 2011). Likewise, osteoprotegerin is also thought to be a regulator of calcification, making it of interest here (Price et al., 2001). Finally, the T-50 test has been shown to correlate strongly with the propensity of blood to form calcifications, wherein a short T-50 is indicative of blood likely to form calcifications, and a lengthening of T50 for patients at risk would be desireable (Pasch et al., 2017).

Hs-CRP is widely acknowledged to be indicative of inflammations of various kinds and if elevated, can signal inflammatory events prior to clinical symptoms.

7. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety and PK of EPN-701 in adult subjects with ESRD on stable hemodialysis.

Primary Objective:

- To determine the safety and tolerability of EPN-701 (administered for two weeks at a daily dose of 10 mg) in subjects with ESRD on stable hemodialysis.

Secondary Objectives:

- To determine, in subjects with ESRD on stable hemodialysis, the plasma levels of the following biomarkers after two weeks of EPN-701 treatment relative to baseline:
  - Uncarboxylated MGP
  - Uncarboxylated osteocalcin
  - Activated Protein C
  - PIVKA-II.

Exploratory Objectives:

- To determine the PK profile of EPN-701 in subjects with ESRD on stable hemodialysis.
- To determine, in subjects with ESRD on stable hemodialysis, the plasma levels of the following biomarkers after two weeks of EPN-701 treatment relative to baseline:
  - Osteoprotegerin
  - Fetuin A
  - High-sensitivity C-Reactive Protein (hs-CRP).
  - Time to Formation of Secondary Calciprotein Particles (T-50 Test); including CPP size.

Specific objectives and corresponding endpoints for the study are outlined (in **Table 2**) below.

Table 2 Study Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Objectives:	
Safety: • To determine the safety and tolerability of EPN-701 (administered for two weeks at a daily dose of 10 mg) in subjects with ESRD on stable hemodialysis.	Primary Safety Endpoint: • Frequency of treatment-emergent adverse events (AEs) and treatment-emergent AEs assessed as related to the study drug (defined as possibly, probably, and definitely related events). A treatment-emergent AE is defined as any AE with an onset between the first dose of the study drug and the last study visit, or any AE with an onset prior to the first dose that increases in severity or frequency after the first dose of study drug. Adverse events include both clinical events and laboratory abnormalities that are assessed as clinically significant. Secondary Safety Endpoints: • Frequency of serious adverse events (SAEs), AEs leading to study drug discontinuation, and AEs of special interest (AESI). • Changes from baseline in laboratory parameters • Changes from baseline in ECG parameters
Secondary Objectives:	
Biomarkers: • To determine, in subjects with ESRD on stable hemodialysis, the plasma levels of the following biomarkers after two weeks of EPN-701 treatment relative to baseline: uncarboxylated MGP; uncarboxylated osteocalcin; Activated Protein C; and PIVKA-II protein.	Biomarker Endpoints: • Biomarker ratios on Day 15 (end-of-treatment) and Day 22 compared to baseline: o Ratio of uncarboxylated to total MGP o Ratio of carboxylated to uncarboxylated osteocalcin o Ratio of carboxylated to uncarboxylated Protein C • Plasma levels of the following biomarkers on Day 15 (end-of-treatment) and Day 22 compared to baseline: o Uncarboxylated MGP o Uncarboxylated osteocalcin o Activated Protein C o PIVKA-II protein

Exploratory Objectives:	
Pharmacokinetics: • To characterize the pharmacokinetic (PK) profile of EPN-701 in in subjects with ESRD on stable hemodialysis.	Pharmacokinetic Endpoints: • EPN-701 plasma concentration at each measured time-point In addition, depending on the observed plasma levels, the following PK parameters may be determined: • Maximum plasma concentration (C_{max}) [ng/mL] • Time to maximum plasma concentration (T_{max}) [hr] • Area under the concentration-time curve (AUC) from time 0 to 24 hours (AUC_{0-24} [hr×ng/mL]).
Biomarkers: • To determine, in subjects with ESRD on stable hemodialysis, the plasma levels of the following biomarkers after two weeks of EPN-701 treatment relative to baseline: osteoprotegerin, Fetuin A, high-sensitivity C-reactive protein (*hs*-CRP) and Time to Formation of Secondary Calciprotein Particles (T-50 Test); including CPP size.	Exploratory Biomarker Endpoints: • Plasma levels of the following biomarkers on Day 15 (end-of-treatment) and Day 22 compared to baseline: ○ Osteoprotegerin ○ Fetuin A ○ *hs*-CRP ○ T-50 Test
Efficacy Objectives:	
Not applicable	Not applicable

8. STUDY DESIGN

8.1 DESCRIPTION OF THE STUDY

This is a Phase 1, prospective, open label study to evaluate the safety, tolerability, and PK of EPN-701, administered once daily for 14 days in subjects with ESRD on a stable hemodialysis regimen. The study will be conducted at one or two dialysis centers in the United States.

A total of 15 consenting subjects meeting the study eligibility criteria will be enrolled and treated with EPN-701 10 mg (one 10 mg capsule to be taken orally once a day, at the same time each morning, for 14 days).

The expected duration of study participation for an individual subject is approximately five weeks, including up to one week for screening, two weeks of study treatment, and two weeks of post-treatment safety follow-up. Subjects will undergo a total of 14 visits during their study participation: Screening visit (within seven days prior to the first dose of study drug), three visits per week during the two-week treatment, and two-week safety follow-up periods (coinciding with the subject's hemodialysis schedule), and the End-of-Study (EOS)/Early Termination visit. Baseline

assessments will be completed prior to the first study drug intake on Day 1. End-of-Treatment (EOT) assessments will be completed after the last dose of study drug on study Day 15 (or earlier in case of an early discontinuation of the study treatment). The EOS/Early Termination visit will occur two weeks after the last dose of study drug (on study Day 29).

Subjects will be monitored for adverse events (AEs), and concomitant medications will be recorded throughout their study participation (from screening through the EOS Visit). Additional safety assessments will include: physical examinations, safety laboratory tests (hematology, including complete blood count [CBC]; complete metabolic panel [CMP, including electrolytes, renal and liver function tests, and lipid profile]; and coagulation panel), and 12-lead electrocardiogram (ECG). In addition, occurrence of dialyzer clotting will be assessed at each dialysis session, and Kt/V (a standard measure of dialysis adequacy) will be calculated at baseline (as the average of the last three pre-study Kt/V values obtained as part of the subject's standard of care), and at EOT (Day 15).

Blood for PK assessments will be sampled pre-dose (pre-dialysis) and post-dose (during and/or at the end of dialysis/before needle removal) on Days 1, 3, 5, 8, 10, 12, and 15, and pre-dose only on Day 17.

Pre- and post-dialysis blood samples for biomarker analyses will be collected at Baseline, and on select Mondays during the two-week treatment, and two-week safety follow-up periods.

Refer to **Table 1**, Schedule of Study Activities for further details.

8.1.1 Schedule of Assessments

A complete schedule of assessments is provided in **Table 1**. A list of assessments to be completed at each study visit is provided in Section 9.5.

8.1.2 Study Committees

An SRC will review the safety data accumulated during the study at regular intervals. The SRC will be comprised of the Sponsor's Medical Monitor, Independent Medical Monitor, and the Principal Investigator. Further details will be provided in the SRC Charter.

8.2 END OF STUDY AND LENGTH OF STUDY

All subjects are expected to be enrolled within approximately three months.

The end of the study is defined as the last subject last visit (LSLV), which is expected approximately six to seven months after the enrollment of the first subject ("first subject in" [FSI]). The actual length of the study will depend on the actual recruitment rate.

In addition, the Sponsor may decide to terminate the study at any time (see Section 9.7.3).

9. MATERIALS AND METHODS

9.1 SUBJECTS

A total of 15 eligible subjects with ESRD on a chronic stable dialysis regimen will be enrolled at one or two dialysis centers in the United States.

9.1.1 Inclusion Criteria

Subjects must meet all inclusion criteria to be enrolled in the study:

1. Male or female ≥18 years of age
2. Diagnosed with ESRD and treated with stable maintenance hemodialysis at least three times a week for at least three months prior to the first dose of study drug. Subjects may have missed (less than or equal to) 4 hemodialysis sessions within three months prior to enrollment, provided that the Principal Investigator deems them suitable for study participation.
3. Clinically stable medical condition, consistent with ESRD, as judged by the investigator based on the results of screening safety evaluations (physical examination, medical history, clinical laboratory tests, vital signs, and 12-lead ECG).
4. Written informed consent
5. Able and willing to comply with the requirements of the study protocol
6. For females of child-bearing potential:
   - Negative serum pregnancy test;
   - Abstinence (refraining from heterosexual intercourse) or use of an acceptable contraception for at least 1 month prior to screening, and willingness to continue for at least 1 month after the last study drug administration.

   A woman is considered to be of childbearing potential if she is post-menarche, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus, or bilateral tubal ligation).

   Examples of acceptable contraceptive methods include: hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

9.1.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria will be excluded from the study:

1. Chronic kidney disease not requiring hemodialysis
2. Acute kidney injury treated with hemodialysis
3. Diagnosis of confirmed calciphylaxis
4. History of any solid organ transplant
5. History of malignancy within 2 years of study enrollment, except for adequately treated carcinoma *in situ* of the cervix and non-melanoma skin carcinoma.

6. History of any major surgery (defined as a surgical procedure involving the cranium, chest, abdomen, or pelvic cavity, or other procedure performed under general anesthesia) within 1 month prior to the first dose of study drug. Subjects with a recent (within <1 month) revision and/or placement of arteriovenous fistula (AVF) will be allowed to participate.
7. History of a major cardiovascular event (such as cerebrovascular accident [CVA], transient ischemic attack [TIA], myocardial infarction, unstable angina) within 1 month prior to the first dose of study drug.
8. Any co-existing disease or condition that may compromise the safety of study participants and/or the integrity of the study, including, but not limited to:
    - Class C or Class D Cirrhosis of the liver
    - Known intestinal malabsorption
    - Inability to take oral medication
9. Life-expectancy <3 months
10. Known history or positive serology for Human Immunodeficiency Virus (HIV), positive serologies of E antigen or with polymerase chain reaction (PCR) positive titers for hepatitis B virus (HBV). Subjects with positive serologies for hepatitis C but with negative PCR for active virus will be allowed.
11. Severe infection requiring intravenous (IV) antibiotics within two weeks prior to the first dose of study drug.
12. Warfarin taken within two weeks prior to the first dose of study drug. Subcutaneous heparin, enoxaparin and novel oral anticoagulants (NOAC; such as apixaban) are permitted.
13. Treatment with an investigational drug within four weeks prior to the first dose of study drug.
14. Pregnancy or lactation.
15. Any other disease or condition which, in the judgment of the Investigator, would place a subject at undue risk by being enrolled in the trial, or cause inability to comply with the trial.

9.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

9.2.1 Randomization and Blinding

Not applicable; this is a non-randomized, uncontrolled, open label study.

9.2.2 Treatment Assignment

After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a subject, the subject will be assigned a unique identification number.

9.3 STUDY DRUG: EPN-701

The term "study drug" or “test product” is used throughout this protocol to refer to EPN-701.

There is no comparator and no other medication use is mandated by the protocol. All concomitant medications will be recorded in the electronic Case Report Form (eCRF).

9.3.1 Description of the Study Drug

EPN-701 is a new formulation containing highly purified MK-7, which belongs to a family of compounds called menaquinones, collectively more commonly-known as vitamin K2.

The drug product is formulated as oral soft-gel capsules. Each capsule contains 10 mg of active ingredient.

Further details are provided in the EPN-701 Investigator's Brochure.

9.3.2 Study Drug Packaging, Storage, and Handling

EPN-701 drug product will be supplied by the Sponsor in bottles with child-resistant caps and tamper-evident, induction-sealed liners. Study drug shipment to a study site will be conditional of the receipt of required approval documents in accordance with applicable regulatory and ethics requirements. Investigators will be provided with sufficient amounts of the study drug to carry out this protocol for the agreed number of subjects.

The EPN-701 drug product will be packaged and labeled by Sherpa Clinical Packaging dba PCI Pharma Services (San Diego, CA). The recommended storage condition for the bottled finished product soft gels is15–30 °C (59-86 °F) (controlled room temperature).

The Investigator has overall responsibility for ensuring that study drug is stored in a secure, limited-access location. Limited responsibility may be delegated to the research pharmacy or member of the study team, but this delegation must be documented.

The study drug must be stored in accordance with labeled storage conditions.

9.3.3 Study Drug Labeling

Each container of study drug will be clearly labeled with study-specific information meeting all applicable regulatory requirements. Clinical trial drug supply labels may bear the following information:

- Statement indicating that the product is limited by federal law to investigational use
- Name, number, or identifying mark of the study drug and quantity of drug in each unit
- Manufacturing date or expiration date of the study drug or re-test date
- Recommended storage conditions for the study drug
- Study drug lot number
- Protocol code or study identification
- Name of the sponsor.

9.3.4 Study Drug Dispensing

The Investigator has overall responsibility for administering/dispensing the investigational product. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the Investigator. This delegation must be documented in the applicable study delegation of authority form.

The Investigator or his/her designee (as documented by the Investigator in the applicable study delegation of authority form) will administer the study drug only to subjects included in this study who have (1) signed the current study-specific informed consent form (ICF); (2) completed all screening assessments and requirements; and (3) met all eligibility criteria for initiation of study treatment.

Each subject will be given sufficient study drug to carry for two weeks. The pharmacist/designee will enter the unique subject identifier and initials on the investigational product bottle/carton label as they are dispensed. At each visit during the treatment period, the study coordinator will verify that the subject is taking the study drug as specified in the protocol.

9.3.5 Study Drug Dosage, Administration, and Compliance

EPN-701, the test product in this study, will be provided by the study sponsor at the following capsule dosage strength:

- 10 mg soft-gel capsule for oral administration.

Each subject will take one 10 mg capsule of EPN-701 per day orally over 14 days.

The study drug is to be taken at the same time each morning. On hemodialysis days (Days 1, 3, 5, 8, 10, and 12), subjects will take their study drug dose pre-dialysis (immediately after needle placement and biomarker sampling, as applicable); on the remaining days during Weeks 1 and 2, subjects will take their study drug dose at home.

Dose modifications of EPN-701 are not permitted during the study.

Any incorrect administration or overdose of the study drug should be noted on the eCRF. Adverse events associated with an incorrect administration or overdose of the study drug should be recorded on the Adverse Event eCRF.

Subject compliance with the study drug schedule must be assessed at the container/packaging level for unused investigational product that is contained within the original packaging, or at the individual count level for opened bottles. The pharmacist/designee will record details on the Study Drug Accountability Form.

9.3.6 Study Drug Accountability

The Investigator or designee will acknowledge receipt of the study drug by documenting shipment content and condition. Any damaged shipments will be replaced and must be reported immediately to the Sponsor. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

Each time study drug is dispensed to a subject or returned, the date, time and amount taken will be documented on the appropriate Study Drug Accountability Form and on the study drug eCRF. The site staff will document the doses taken in clinic on the subject's drug accountability source documentation. Doses taken at home (including date, time, and amount taken) will be documented by the subject on the Study Drug Home Intake Form. Subjects will be asked to return the completed Study Drug Home Intake Form to the clinic at each scheduled visit so that the study coordinator can document all study drug intakes in the subject's source documents and enter on the e-CRF. The final Study Drug Home Intake Form will be collected from the subject after the last dose has been taken and will be placed in the subject's study chart. The CRA will verify the study drug eCRF entries against the Study Drug Accountability Form and source documents to ensure consistency.

No investigational product stock or returned inventory from this study may be removed from the site where originally shipped without prior knowledge and consent by the Sponsor. If such transfer is authorized by the Sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The Sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the Sponsor, all unused stock, and empty/used investigational product packaging are to be sent to a designated contractor on behalf of the Sponsor. Investigational product being returned to the Sponsor's designated contractors must be counted and verified by clinical site personnel and the Sponsor (or designated Contract Research Organization [CRO]). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken, and the labeled amount is to be documented in lieu of counting. All certificates of delivery/drug receipts should be signed by the site representative to confirm contents of shipment. Shipment return forms, when used, must be signed prior to shipment from the site. Returned investigational product must be packed in a tamper-evident manner to ensure product integrity. The Sponsor must authorize the return of any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

All study drugs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Study Drug Accountability Form.

9.3.7 Post-Trial Access to EPN-701

Not applicable.

9.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription and over-the-counter drugs, vaccines, and nutritional supplements) used by a subject in addition to the study drug from the screening to the EOS/Early Termination visit. All such medications should be recorded on the Concomitant Medications eCRF.

9.4.1 Prohibited Therapy

Patients receiving long-term warfarin (Coumadin) frequently develop asymptomatic excessive prolongation of their international normalized ratio (INR) results. The anticoagulant effect of warfarin, functioning by its interference with the clotting effect of vitamin K, can be offset with as little as 1 mg of vitamin K (Crowther et al. 1998). Therefore, use of vitamin K is contraindicated in individuals on warfarin therapy (Vitamin K2 Monograph, 2009).

Medications that are prohibited while the subject is receiving study drug are listed in **Table 3**.

Table 3 Washout Periods for Prohibited Medications

Prohibited Medication	Minimum Washout Period Prior to the First Dose of Study Drug
Any investigational therapy	4 weeks
Warfarin*	2 weeks
IV antibiotics	2 weeks
Prescription and non-prescription medications known to be sensitive substrates of CYP3A** or CYP4F2***	None
Herbal and homeopathic remedies	None

Abbreviations: IV=intravenous

* Subcutaneous heparin, enoxaparin and novel oral anticoagulants (NOAC; such as apixaban) are permitted.

** As listed in the FDA *Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers* (2017)

*** Example: fingolimod

The investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

9.4.1.1 Herbal Therapies

The use of herbal therapies will be prohibited during the study.

9.4.2 Prohibited Food

No foods are prohibited during treatment with the study drug.

9.5 STUDY VISITS

The schedule of assessments to be performed during the study is provided in **Table 1**. All activities must be performed and documented for each subject.

The expected duration of study participation for an individual subject is approximately five weeks, including up to one week for screening, two weeks of study treatment, and two weeks of post-treatment safety follow-up.

Subjects will undergo a total of 14 visits during their study participation: Screening visit (within seven days prior to the first dose of study drug), three visits per week during the two-week treatment, and two-week safety follow-up periods (coinciding with the subject's hemodialysis schedule), and the EOS/Early Termination visit. Baseline assessments will be completed prior to the first study drug intake on Day 1. The EOS/Early Termination visit will occur two weeks after the last dose of study drug (on study Day 29).

Subjects will be closely monitored for safety and tolerability throughout the study. At each treatment visit, assessments should be completed prior to the study drug administration, unless otherwise stated.

At each study visit, subjects will also undergo hemodialysis, as per their standard ESRD management; hemodialysis is therefore not listed as a study-related assessment in the following sections.

9.5.1 Screening Visit (Day -7 to Day -1)

Subjects will undergo the following assessments during screening:

- Obtaining informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization (see Section 9.6.1 for details)
- Review of eligibility (inclusion and exclusion) criteria (see Sections 9.1.1 and 9.1.2 for details)
- Recording of general medical history (including menstrual history for females of childbearing potential), disease history, and demographics (see Section 9.6.2 for details)
- Recording of baseline and concomitant medications (see Section 9.6.3 for details)
- Complete physical examination, measurement of height and weight (see Section 9.6.4 for details)
- Standard 12-lead ECG within 60 minutes pre-dialysis (see Section 9.6.6 for details)
- Measurement of vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature (pre-dialysis) (see Section 9.6.5 for details)
- Testing for HIV, hepatitis B and C (see Section 9.6.8.1 for details)
- Collection of blood samples for safety laboratory tests pre-dialysis (hematology, CMP, coagulation panel, and serum β-hCG pregnancy test (females of childbearing potential only) (see Section 9.6.8.1 for details).

9.5.2 Visit 1 (Day 1, Baseline), Visit 4 (Day 8), Visit 7 (Day 15, End-of-Treatment), and Visit 10 (Day 22) [Mondays]

Subjects will undergo the following assessments during these visits:

- (At baseline/Visit 1 only:) Review of eligibility (inclusion and exclusion) criteria (see Sections 9.1.1 and 9.1.2 for details)
- Recording of any changes in concomitant medications (see Section 9.6.3 for details)
- (At Visit 7 only, if clinically indicated:) Symptom-driven physical examination (see Section 9.6.4 for details)
- (At Visits 1, 4, and 7): Measurement of body weight within 60 minutes pre-dialysis and within 60 minutes post-dialysis (see Section 9.6.4 for details)
- (At Visit 7 only): Standard 12-lead ECG within 60 minutes pre-dialysis (see Section 9.6.6 for details)
- (At Visits 1, 4, and 7): Measurement of vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature within 30 minutes pre-dialysis and within 30 minutes post-dialysis (see Section 9.6.5 for details)
- Collection of blood samples for safety laboratory tests pre-dialysis (hematology, CMP, coagulation panel) (see Section 9.6.8.1 for details)
- (At Visits 1, 7, and 10): Collection of blood samples for biomarker assessments pre-dialysis (pre-dose) (see Section 9.6.8.2 for details):
  - MGP, osteocalcin, Protein C, PIVKA-II protein, Fetuin A, osteoprotegerin, *hs*-CRP, and Time to Formation of Secondary Calciprotein Particles (T-50 Test); including CPP size.
- Collection of blood samples for PK assessments pre-dialysis/pre-dose (at the time of needle placement) (Visits 1, 4, and 7), during dialysis (Visits 1 and 4) and at the end of dialysis (before needle removal) (Visits 1, 4 and 7) (see Section 9.6.8.3 for details)
- (At Visits 1 and 4 only): Study drug administration pre-dialysis (immediately after needle placement and the pre-dialysis biomarker sampling) (see Section 9.3.5 for details)
- Recording of changes in baseline complaints under general medical history (events occurring before the first dose of study drug [Visit 1 only]; see Section 9.6.2 for details) or AEs (events occurring after the first dose of study drug [Visit 1 post-dose and subsequent visits]; see Section 10.3 for details). Any occurrence of dialyzer clotting (assessed at each dialysis session) is to be recorded as an AE (see Section 10.3.2).
- Kt/V will be calculated at baseline as the average of the last three pre-study Kt/V values obtained as part of the subject's standard of care. At Visit 7, Kt/V will be measured and compared with the baseline value.

Assessments completed after the last dose of study drug on study Day 15/Visit 7 (or earlier in case of an early discontinuation of the study treatment) will be considered EOT assessments.

At the end of Visit 1, subjects will receive a sufficient supply of the study drug for two weeks of treatment.

9.5.3 Visits 2 & 3 (Days 3 & 5), Visits 5 & 6 (Days 10 & 12), Visits 8 & 9 (Days 17 & 19), and Visits 11 & 12 (Days 24 & 26) [Wednesdays & Fridays]

Subjects will undergo the following assessments during these visits:

- Recording of any changes in concomitant medications (see Section 9.6.3 for details)
- Recording of AEs (see Section 10.3 for details). Any occurrence of dialyzer clotting (assessed at each dialysis session) is to be recorded as an AE (see Section 10.3.2).
- (At Visits 2, 3, 5, and 6): Measurement of body weight within 60 minutes pre-dialysis and within 60 minutes post-dialysis (see Section 9.6.4 for details)
- (At Visits 2, 3, 5, and 6): Measurement of vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature within 30 minutes pre-dialysis and within 30 minutes post-dialysis (see Section 9.6.5 for details)
- (Visits 2, 3, 5, and 6 only:) Study drug administration pre-dialysis (immediately after needle placement) (see Section 9.3.5 for details)
- Collection of blood samples for PK assessments pre-dialysis/pre-dose (at the time of needle placement) (Visits 2, 3, 5, 6, and 8), and at the end of dialysis (before needle removal) (Visits 2, 3, 5, and 6) (see Section 9.6.8.3 for details).

9.5.4 End-of-Study/Early Termination Visit (Day 29)

Subjects will undergo the following assessments during these visits:

- Recording of any changes in concomitant medications (see Section 9.6.3 for details)
- Recording of AEs (see Section 10.3 for details)
- Complete physical examination (see Section 9.6.4 for details)
- Standard 12-lead ECG within 60 minutes pre-dialysis (see Section 9.6.6 for details)
- Measurement of body weight within 60 minutes pre-dialysis and within 60 minutes post-dialysis (see Section 9.6.4 for details)
- Measurement of vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature within 30 minutes pre-dialysis and within 30 minutes post-dialysis (see Section 9.6.5 for details)
- Collection of blood samples pre-dialysis for safety laboratory tests (hematology, CMP, coagulation panel) (see Section 9.6.8.1 for details).

9.6 STUDY ASSESSMENTS

9.6.1 Informed Consent Forms and Subject Log

Written informed consent for participation in the study must be obtained from all prospective subjects before performing any study-specific screening test or procedure. The investigator will maintain a log of all subjects who consented to participating in the study.

9.6.2 Medical History and Demographic Data Collection

Details of the underlying condition (including ESRD and dialysis history), as well as general medical history (including clinically significant diseases or conditions, surgeries, and reproductive status), will be recorded at screening/baseline. Baseline complaints (symptoms or adverse experiences present prior to the first dose of study drug) will also be recorded as medical history.

Demographic data will include age, sex, and self-reported race/ethnicity.

9.6.3 Baseline and Concomitant Medications

All medications (including over-the-counter medications) or therapy administered to the subject during the 30 days prior to the first dose of study drug will be recorded at screening/baseline (including start date, medication name, dosage, frequency, and route of administration). Any contraindicated medications will be stopped or replaced by different medication and the subject will be required to observe the protocol-specified wash-out period (refer to Section 9.4.1 for details).

Any changes to concomitant medications will be documented regularly throughout the study.

9.6.4 Physical Examinations and Measurements

A complete physical examination (including a review of the main body organs and systems) must be conducted at screening and the EOS/Early Termination visit (Day 29). In addition, a symptom-driven (abbreviated) physical exam may be performed at the End-of-Treatment (EOT) visit (Day 15), if the investigator deems it clinically indicated; see **Table 1**.

Any treatment-emergent clinically significant physical examination findings should be recorded as adverse events on the Adverse Event CRF.

Subjects will also undergo body weight and height measurement at screening/baseline, and body weight measurements (as part of their standard care on dialysis days) within 60 minutes pre-dialysis and within 60 minutes post-dialysis on each dialysis day during the 2-week treatment period (Visits 1 through 6), at the EOT visit (Day 15), and at the EOS visit (Day 29); see **Table 1**.

9.6.5 Vital Signs Measurements

Vital signs (including blood pressure, heart rate, respiratory rate, and oral body temperature) will be measured at screening, and (as part of their standard care on dialysis days) within 30 minutes pre-dialysis and within 30 minutes post-dialysis at each treatment visit (Visits 1 through 6), at the EOT visit (Day 15), and at the EOS visit (Day 29); see **Table 1**. Any treatment-emergent clinically significant vital signs abnormalities should be recorded as adverse events on the Adverse Event CRF.

9.6.6 Electrocardiograms

Standard 12-lead ECG recordings will be obtained within 60 minutes pre-dialysis at screening/baseline, at the EOT visit (Day 15), and at the EOS visit (Day 29); see **Table 1**. ECG

recordings must be performed after the subject has been resting in a supine position for at least 5 minutes, and prior to other procedures scheduled at that same time (e.g., blood draws).

The Principal Investigator must review, interpret sign, and date all ECG tracings. ECG abnormalities must be documented on the CRF and assessed for clinical significance. All treatment-emergent clinically significant ECG abnormalities must be reported as AEs.

Paper copies of ECG tracings will be kept as part of the subject's file at the site.

9.6.7 Assessment of Dialysis Adequacy (Kt/V)

Kt/V is a standard measure of dialysis adequacy, where *K* stands for the dialyzer urea clearance, *t* stands for the duration of the dialysis session, and *V* stands for the volume of urea distribution (roughly corresponding to the volume of water contained in the patient's body).

As part of the safety evaluations, Kt/V will be measured at EOT (Day 15), and compared to the baseline value, which will be calculated as the average of the last three pre-study Kt/V values obtained as part of the subject's standard of care. In case the Kt/V value obtained at EOT is reduced compared to baseline (pre-study measurements), the Investigator will determine (in consultation with the Medical Monitor, as needed) if the event qualifies for reporting as an AE.

9.6.8 Laboratory, Biomarker, and PK Samples

The assessments listed in this section will be performed at Covance Central Laboratory Services (Covance). Instruction manuals and supply kits will be provided by Covance for all central laboratory assessments.

An overview of the standard safety laboratory, biomarker, and PK sampling requirements is provided below. For additional details on laboratory assessments and sample handling, refer to the laboratory manual.

9.6.8.1 Safety Laboratory Assessments

Samples for the following safety laboratory tests will be sent to the central laboratory for analysis:

- Hematology panel: red blood cell (RBC) count, hemoglobin, hematocrit, and white blood cell (WBC) count, with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), if clinically indicated.
- Complete Metabolic Panel (CMP):
  - Glucose, albumin, total protein;
  - Electrolytes: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphate;
  - Renal function tests: blood urea nitrogen (BUN), creatinine;
  - Liver function tests: (ALT, AST, bilirubin), and
  - Lipid profile: total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG).
- Coagulation panel includes: partial thromboplastin time (PTT), INR, and platelet count.

All blood sampling will occur pre-dialysis (at the time of needle placement).

In addition, all subjects will undergo the following tests at screening only:

- Serology for:
  - HIV
  - HBV: hepatitis B “e” antigen (HBeAg) and PCR for the active virus (HBV deoxyribonucleic acid [DNA]); and
  - HCV: HCV antibody and PCR for active virus (HCV ribonucleic acid [RNA])
- For women of child bearing potential only: serum beta-human chorionic gonadotropin (β-hCG) pregnancy test (the results of the screening pregnancy test must be negative for enrolment).

The schedule for laboratory assessments is provided in **Table 1**. All baseline laboratory assessments may occur during screening (within 7 days prior to the first dose of the study drug).

The total volume of blood drawn from each subject for safety laboratory assessment will be approximately 57 mL over the course of the study. Instructions for safety laboratory specimen collection, handling, and shipping will be included in the laboratory manual provided by the Central Laboratory (Covance).

9.6.8.2 Biomarker Assessments

Blood samples will be obtained for biomarker evaluation according to the schedule in **Table 1** and **Table 4**. Serially collected blood samples will be processed to obtain plasma for the determination of the following biomarkers:

- Uncarboxylated MGP; uncarboxylated osteocalcin; Activated Protein C, PIVKA-II protein; Fetuin A, osteoprotegerin, *hs*-CRP, and Time to Formation of Secondary Calciprotein Particles (T-50 Test); including CPP size.

Blood sampling for biomarker analysis will always occur pre-dialysis (at the time of needle placement): on Day 1 (Baseline), Day 15 (EOT), and Day 22 (1 week after the last study drug dose).

The total volume of blood drawn from each subject for biomarkers assessment will be approximately 48 mL over the course of the study (approximately 16 mL per assessment time-point). Instructions for biomarker specimen collection, handling, and shipping will be included in the laboratory manual provided by the Central Laboratory (Covance).

Table 4 Biomarker Assessments

Sample Type	Timing	Biomarkers
Blood	Day 1, pre-dialysis* (Week 1, Baseline)	Uncarboxylated MGP; unccarboxylated osteocalcin, Activated Protein C, PIVKA-II protein, Fetuin A, osteoprotegerin, *hs*-CRP, and Time to Formation of Secondary Calciprotein Particles (T-50 Test); including CPP size.
Blood	Day 15, pre-dialysis* (EOT)	Uncarboxylated MGP; unccarboxylated osteocalcin, Activated Protein C, PIVKA-II protein, Fetuin A, osteoprotegerin, *hs*-CRP, and Time to Formation of Secondary Calciprotein Particles (T-50 Test); including CPP size.
Blood	Day 22, pre-dialysis* (1 week after the last study drug dose)	Uncarboxylated MGP; unccarboxylated osteocalcin, Activated Protein C, PIVKA-II protein, Fetuin A, osteoprotegerin, *hs*-CRP, and Time to Formation of Secondary Calciprotein Particles (T-50 Test); including CPP size.

CPP=calciprotein particles; EOT=end-of-treatment; hs-CRP= high-sensitivity C-Reactive Protein; MGP=matrix gamma-carboxyglutamic acid (Gla) protein; PIVKA-II=Protein Induced in Vitamin K Absence/Antagonist-II; T-50=Time to Formation of Secondary Calciprotein Particles.

* Pre-dialysis=at the time of needle placement

9.6.8.3 Pharmacokinetic Assessments

Blood for PK assessments will be sampled as follows:

- On Visit 1/Day 1 (baseline) and Visit 4/Day 8 (Week 2, on-treatment): pre-dialysis (at the time of needle placement; denoted as 0 hours), followed by study drug administration, and then at 1 hour (+/- 5 minutes), 2 hours (+/- 5 minutes), 3 hours (+/- 5 minutes), 4 hours (+/- 30 minutes)/before needle removal, 6 hours (+/- 30 minutes), 8 hours (+/- 30 minutes), and 24 hours (+/- 60 minutes) after study drug administration;
- On Visit 2/Day 3, Visit 3/Day 5, Visit 5/Day 10, Visit 6/Day 12, and Visit 7/Day 15: pre-dialysis (at the time of needle placement, at 0 hours), immediately followed by study drug administration, and then at 4 hours (+/- 30 minutes)/ before needle removal; and
- On Visit 8/Day 17 (Week 3, off-treatment): pre-dialysis only (at the time of needle placement).

The timing and sequence of PK blood sample collections relative to the study drug administrations and dialysis will be as follows:

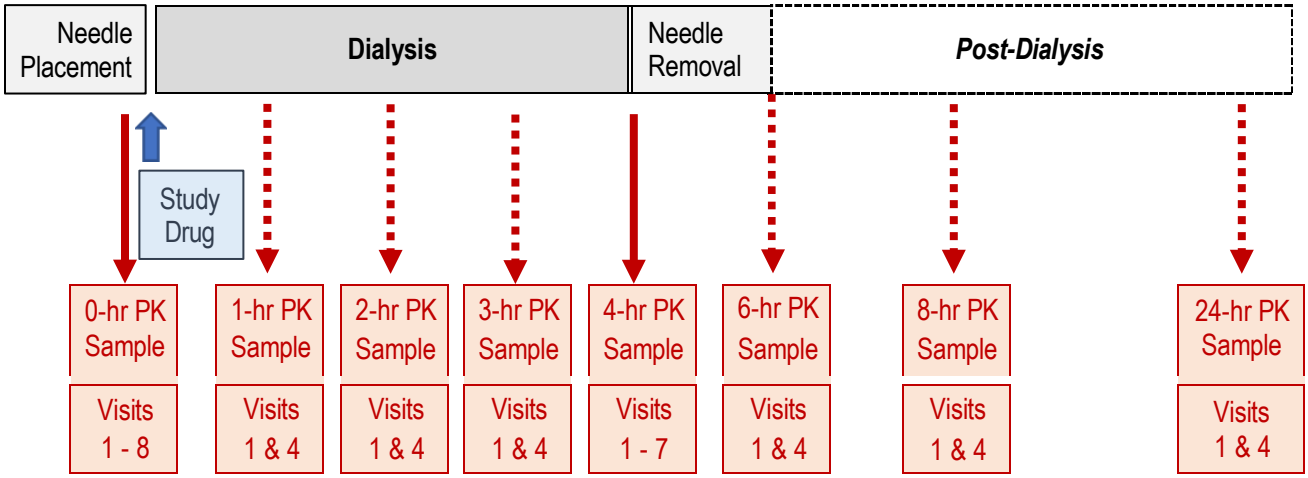
- PK samples taken pre-dialysis (pre-dose; at 0 hour): Samples will be collected after needle placement and will be immediately followed by the study drug administration. Immediately following drug administration, dialysis is to be started.
- PK samples taken during dialysis (post-dose): Samples will be collected at 1 hour (+/- 5 minutes), 2 hours (+/- 5 minutes) and 3 hours (+/- 5 minutes) after the 0-hour PK time-point.

- PK samples taken post-dialysis (post-dose): Samples will be collected when the dialysis is completed (before needle removal) or at 4 hours (+/- 30 minutes) after the 0-hour PK time-point, whichever occurs first.
- Note: The duration of dialysis sessions is expected to be approximately 4 hours; however, the actual duration should not have an impact on the PK sample collection time-points.

The calendar date and actual clock time will be recorded for each PK blood sample collection and the actual elapsed time from dosing will be used for the PK calculations.

Refer to **Figure 5** for further details.

Figure 5 – Sequence of PK Sampling, Visits 1 – 8



Plasma samples will be assayed for EPN-701 concentrations (ng/mL) according to standard procedures, using a validated high-performance liquid chromatography (HPLC) tandem mass spectrometric (LC/MS/MS) method.

Apart from the plasma concentrations at each time-point, depending on the observed levels, the following PK parameters may also be determined:

- Maximum plasma concentration (C_{max}) [ng/mL]
- Time to maximum plasma concentration (T_{max}) [hr]
- Area under the concentration-time curve (AUC) from time 0 to 24 hours (AUC_{0-24} [hr×ng/mL]).

The total volume of blood drawn from each subject for PK assessment will be approximately 108 mL over the course of the study (approximately 4 mL per assessment time-point). Instructions for PK specimen collection, handling, and shipping will be included in the laboratory manual provided by the Central Laboratory (Covance).

9.6.9 Efficacy Evaluations

Not applicable.

9.7 TREATMENT, SUBJECT, SITE, AND STUDY DISCONTINUATION

9.7.1 Study Drug Discontinuation

Premature discontinuation of the study drug by the Investigator should be discussed whenever possible with the Medical Monitor before the subject stops taking the study drug.

Potential reasons for permanent discontinuation of the study drug are detailed in Section 9.7.2.1. The primary reason for study drug discontinuation should be documented on the appropriate eCRF along with the date of stopping the study drug, and the total amount of the study drug taken. If the study drug is discontinued, regardless of the reason, the end-of-treatment evaluations are to be performed as completely as possible.

9.7.2 Withdrawal of Subjects from the Study

A subject may voluntarily withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. In addition, the Investigator or Sponsor may withdraw the subject at any time (e.g., in the interest of subject safety).

To the extent feasible, all withdrawn subjects should undergo the protocol-specified post-treatment follow-up. However, subjects will not be followed for any reason after consent has been withdrawn.

The reason for withdrawal from the study must be determined by the Investigator and recorded in the subject's medical record and on the eCRF. If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF. If an AE is (one of) the reason(s) for discontinuation, then "Adverse event" must be recorded as the reason for discontinuation on the eCRF. Any comments (spontaneous or elicited) pertinent to the withdrawal or complaints made by the subject must be recorded in the source documents.

9.7.2.1 Reasons for Study Drug Discontinuation and Withdrawal

Reasons for discontinuation from the study drug and for withdrawal from the study include but are not limited to:

- Adverse event
- Any medical condition that may jeopardize the subject's safety
- Significant worsening in the subject's underlying condition
- Withdrawal of consent by the subject
- Protocol violation (such as subject non-compliance with the study drug or study procedures, use of prohibited medication)
- Subject lost to follow-up
- Pregnancy.

For any subject lost to follow-up, at least three documented attempts must be made to contact the subject prior to the last protocol-mandated study visit. One of these documented attempts must include a written communication sent to the subject's last known address via courier or mail with an acknowledgement of receipt request.

9.7.2.2 Replacement of Subjects

Subjects prematurely discontinuing study drug or withdrawing from the study (while on treatment or during the 2-week post-treatment safety follow-up) may be replaced if the following criteria are met:

- If a subject discontinues study drug or withdraws from the study for any reason on or before Day 22.
- If a subject misses a visit(s) due to non-compliance, SAE and/or hospitalization at a critical PK and/or biomarker timepoint(s) as it relates to the study endpoint.

A decision to replace subject(s) will be determined by the Sponsor and communicated to the Principal Investigator/Site with rationale and further instruction, as applicable.

9.7.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. The Sponsor will notify the investigator(s) in case a decision is made to discontinue the study.

9.7.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonization (ICH) guideline for Good Clinical Practice
- Study activities completed (i.e., all subjects have completed the study and all obligations have been fulfilled.).

10. ASSESSMENT OF SAFETY

10.1 DEFINITIONS

An **Adverse Event (AE)** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a

medicinal (investigational) product, whether related to the medicinal (investigational) product or not (ICH Guidance E2A 1994).

Treatment-emergent AEs are defined as any AE with an onset between the first dose of the study drug and the last study visit, or any AE with an onset prior to first dose that increases in severity or frequency after the first dose of study drug.

A **Serious Adverse Event (SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening [1]
- Requires inpatient hospitalization or prolongation of existing hospitalization [2]
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event [3]

[1] The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

[2] Hospitalizations which are the result of elective or previously scheduled surgery for pre-existing conditions, where such conditions have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE. However, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meets serious criteria must be reported as SAE(s).

[3] Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

Note:

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe; see Section 10.3.3.1); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Adverse events of special interest (AESI): An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

The following events will be considered AESIs in this study:

- Treatment-emergent ALT or AST >3 x upper limit of normal (ULN) in combination with (1) total bilirubin >2 x ULN and/or (2) clinical jaundice.

Clinically significant laboratory, ECG, or vital signs abnormalities: A laboratory test or ECG abnormality is deemed clinically significant if it meets one or more of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., study drug interruption or discontinuation, or dosage modification)
- Results in a medical intervention (e.g. treatment) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment.

Study Drug Misuse is defined as intentional use of the investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).

Overdose is an intentional or unintentional intake of a dose of the investigational product exceeding the pre-specified total daily dose of the product.

Medication Error is an error made in prescribing, dispensing, administration, and/or use of an investigational product.

10.2 OVERALL SAFETY PLAN

The safety plan for this study is based on clinical experience with MK-7 in published clinical studies. The anticipated safety risks for EPN-701 are outlined in Section 6.3.4. Please refer to the EPN-701 Investigator's Brochure for a complete summary of clinical safety information.

Several measures will be taken to ensure the safety of subjects participating in this study. These include the pre-specified eligibility criteria (see Section 9.1.1 and Section 9.1.2), designed to exclude subjects at higher risk for adverse events, close safety monitoring of subjects during the study (see Section 9.5), including assessment of the nature, frequency, and severity of adverse events (see Section 10.3).

General safety assessments will consist of monitoring and recording adverse events, including SAEs, AESIs, and AEs leading to study drug discontinuation (with or without withdrawal from the study), performing protocol specified physical examinations, ECGs and safety laboratory assessments (including hematology, CMP, and coagulation panel), and measuring vital signs; see **Table 1** for the list and timing of study assessments. During on-treatment study visits, applicable clinical and laboratory assessments will be completed and reviewed prior to study drug administration. Adverse events (regardless of relationship to study drug) will be recorded in the AE CRF for 14 days after the last dose of EPN-701 (until the EOS Visit/Day 29), and will be graded by severity, and assessed for causality. Serious adverse events (SAEs), AESIs and pregnancies occurring during or within 30 days after the last dose of EPN-701 will be reported in an expedited

fashion, as described in Section 10.4. Any case of study drug error, misuse, or overdose will also be reported in an expedited fashion (see Section 10.4).

A SRC will review the safety data accumulated during the study at regular intervals. The SRC will be comprised of the Sponsor's Medical Monitor, Independent Medical Monitor, and the Principal Investigator; refer to Section 10.6.

10.2.1 Dose Modifications and Interruptions due to Adverse Events

Dose reduction of EPN-701 is not permitted in this study.

There are currently no known adverse events that would require interruption or discontinuation of EPN-701 treatment. However, unanticipated adverse events or other safety findings during the trial may warrant interruption or discontinuation of study drug. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

10.3 RECORDING AND ASSESSMENT OF ADVERSE EVENTS

The investigator is responsible for ensuring that all adverse events are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 10.4 (immediate reporting).

For each adverse event, the investigator will make an assessment of seriousness (see Section 10.1 for seriousness criteria), severity (see Section 10.3.3.1), and causality (see Section 10.3.3.2) on the Adverse Event eCRF.

10.3.1 Adverse Event Recording and Reporting Period

All AEs with an onset between the time the informed consent is signed and 14 days after the last dose of study drug (EOS/Early Termination Visit) are to be recorded on the appropriate Adverse Event CRF pages and in source documents.

Serious adverse events (SAEs), AESIs and pregnancies occurring during or within 30 days after the last dose of EPN-701 will also be reported in an expedited fashion, as described in Section 10.4. SAEs and AESI considered to be related to the study drug by the investigator, will be reported to the Sponsor even if they occurred after the protocol-specified reporting period (i.e., more than 30 days after the last dose of EPN-701). Follow-up of SAEs and AESIs will continue until resolution or until they reach a chronic/stable condition. In the unlikely event of a pregnancy reported during the study, the event should be followed until pregnancy outcome, i.e. birth or termination.

10.3.2 Adverse Event Recording Guidelines

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Colloquialisms and abbreviations should be avoided.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

The following guidelines should be observed when recording AEs:

- Preexisting medical conditions (present at the screening visit): should be recorded on the Medical History eCRF. A preexisting medical condition should be recorded as an AE only if the frequency or severity worsens during the study.
- Symptoms of the Disease Under Study: should not be recorded as AEs, as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening of the symptoms should be recorded as an AE.
- Diagnosis vs Symptoms: Where possible, a diagnosis, rather than a list of symptoms, should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.
- Secondary AEs: In general, adverse events that are secondary to other events (e.g., clinical sequelae or cascade events) should be identified by their primary cause, except for severe or serious secondary events. If it is unclear as to whether the events are associated, each AE should be recorded separately on the Adverse Event eCRF.
- Persistent AEs (events that extends continuously between study visits): should only be recorded once, with the highest overserved/reported severity on the Adverse Event eCRF.
- Recurring AEs (events that resolves between study visits and subsequently recur): each recurrence should be recorded as a separate event on the Adverse Event eCRF.
- Abnormal laboratory values: All clinically significant laboratory test results must be reported as AEs. If a clinically significant laboratory abnormality is a sign of a disease or syndrome, only the diagnosis should be recorded on the Adverse Event eCRF.
- Abnormal ECG results: All treatment-emergent clinically significant ECG abnormalities must be reported as AEs.
- Adverse events associated with an incorrect administration (medication error or misuse) or overdose of the study drug should be recorded on the Adverse Event eCRF. Any incorrect administration of study drug or study drug overdose should be noted on the Study Drug Administration CRF and reported as a protocol deviation.
- Any occurrence of dialyzer clotting (assessed at each dialysis session) is to be recorded as an AE, using the term “clotting of extracorporeal circuit" or equivalent.

10.3.3 Assessment of Adverse Events

10.3.3.1 Assessment of Severity

The medical assessment of AE severity is determined by using the following definitions:

- **Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- **Moderate:** A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- **Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

The severity of AEs must be assessed during the course of the event. An event that continues, but changes in severity over a period of time should be captured once on the AE eCRF form, with the highest severity reported though its duration. Worsening of pre-treatment events after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of the investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the AE eCRF).

10.3.3.2 Assessment of Causality

The causality assessment for each AE must be completed by the investigator. The investigator should use medical judgment, including knowledge of the subject, the circumstances surrounding the event, and evaluate any potential alternative causes when deciding whether there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, the AE should be classified as 'not related'. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, the AE should be assessed as 'related'. The causality assessment must be documented in the source document and the CRF.

Table 5 Guidance for the Assessment of Adverse Event Causality

Term	Relationship	Definition
Definitively Related	Yes	A clinical event, including laboratory test abnormality that occurs in an apparent time sequence to the administration of the investigational product, is plausible pharmacologically, and cannot be explained by concurrent disease or other drugs or chemicals. Withdrawal of the drug (dechallenge) was followed by improvement or resolution of the event. Recurrence of symptoms on rechallenge (if performed) has occurred.
Probably Related	Yes	A clinical event, including laboratory test abnormality, with a reasonable time sequence to the administration of the investigational product, unlikely to be attributed to concurrent disease or other drugs or chemicals. Withdrawal of the drug (dechallenge) was followed by improvement or resolution of the event. Rechallenge information is not required to fulfil this definition.

Term	Relationship	Definition
Possibly Related	Yes	A clinical event, including laboratory test abnormality, for which a time relationship with the administration of the investigational product may exist, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely Related	No	A clinical event, including laboratory test abnormality, with a doubtful temporal relationship to the administration of the investigational product, and in which other concomitant drugs, chemicals or the subject's underlying disease provide plausible explanations for the event.
Not Related	No	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

The investigator's assessment of the relationship between the AE and the underlying condition (including hemodialysis) will also be recorded.

10.3.3.3 Assessment and Documentation of Outcome

During the study period, resolution of AEs (with dates) should be documented on the AE eCRF and in the subject's medical record to facilitate source data verification.

The outcome of AEs must be recorded during the study on the CRF by selecting one of the following options:

- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Ongoing, but reached chronic or stable condition at the last follow-up
- Fatal
- Unknown

10.3.4 Adverse Event Follow-up Period

The investigator should follow each AE until the event has resolved to baseline or normal status, the event is assessed as stable by the investigator (no further improvement or worsening of the event is expected), the subject is lost to follow-up, or the subject withdraws consent. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

Every effort should be made to follow all SAEs until a final outcome can be determined.

In the unlikely event of a pregnancy reported during the study, the event should be followed until pregnancy outcome, i.e. birth or termination.

10.4 IMMEDIATE REPORTING REQUIREMENTS

10.4.1 Immediately Reportable Events

The investigator must report the following events to the Sponsor immediately (i.e., within 24 hours of becoming aware of the event), regardless of their relationship to study drug:

- SAEs
- AESIs
- Pregnancies
- Medication errors, misuses, and overdoses.

10.4.2 Reporting Requirements for SAEs and AESIs

10.4.2.1 Serious Adverse Event Reporting Timeframe

All SAEs and AESIs (regardless of their relationship to the study drug) occurring from the time the subject provided informed consent until 30 days after the last dose of study drug must be reported to the designated Pharmacovigilance Department within 24 hours of the first awareness of the event. Thereafter, any SAE(s) or AESI considered "related" to the study drug must be reported to the Pharmacovigilance Department within 24 hours of the first awareness of the event regardless of how much time has elapsed since the last dose of the study drug.

Preferred method: The investigator should report these events either by scanning and emailing the completed Serious Adverse Event/Adverse Event of Special Interest Reporting Form to the following e-mail address:

epizonsafety@medassessment.com

Alternative method: The completed Serious Adverse Event/Adverse Event of Special Interest Reporting Form may be faxed to the following designated fax number:

1-949-369-9242

Attention: Epizon Safety

Reports should be accompanied by all relevant supplemental material. Receipt will be acknowledged in a timely manner via secure email.

Electronic data capture (EDC) is the primary source for entering SAE data documented on source documents. However, a back-up SAE Form (and Guidelines) for SAE reporting should be used for reporting to the Safety group within the SAE Reporting Guidelines in the event EDC is down or not accessible.

The investigator must also report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information may include any of the following:

- Change in the event's outcome (including resolution)

- Change in the diagnosis
- Development of new signs or symptoms or significant worsening in the condition
- Significant new test results
- Change in causality based on new information
- Other significant information on the clinical course of the event.

Investigators must also comply with local requirements for reporting SAEs to the Institutional Review Board (IRB).

The onset date of the SAE is the date that symptoms of the event began, and the resolution date is the date the symptoms resolve, or the event is considered to have reached a chronic/stable condition.

Any SAE that results in the subject's death must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

10.4.3 Reporting Requirements for Pregnancies

All pregnancies detected from the time informed consent is signed until 30 days after the last dose of study drug are to be reported.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours from learning about the event using the Pregnancy Report Form. If a pregnancy is detected during the study, the subject will be immediately withdrawn.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum (or termination of the pregnancy).

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) using the Clinical Trial Serious Adverse Event Form. An elective abortion is not considered an SAE.

In addition, if the Investigator determines that the pregnancy meets seriousness criteria, it must be reported as an SAE. The test date of the first positive serum/urine HCG test or ultrasound result will determine the pregnancy onset date.

10.5 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, AND INSTITUTIONAL REVIEW BOARDS

The Sponsor will promptly evaluate all SAEs and AESIs against the existing cumulative knowledge about the investigational product to identify and expeditiously communicate possible

new safety findings to investigators, Institutional Review Boards (IRBs), and the US Food and Drug Administration (FDA), as per the applicable regulations and guidelines.

Reporting requirements to the FDA and IRB(s) will be based on the investigator's assessment of causality and seriousness, and the Sponsor's assessment of the expectedness of the event. Expectedness will be evaluated by comparing the severity of the event (and cumulative event frequency observed in the study, as applicable) with the severity and frequency reported in the applicable reference document (EPN-701 Investigator's Brochure).

10.6 SAFETY REVIEWS BY THE STUDY SRC

A SRC will review the safety data accumulated during the study at regular intervals. The SRC will be comprised of the Sponsor's Medical Monitor, Independent Medical Monitor, and the Principal Investigator. Further details will be provided in the SRC Charter.

11. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

11.1 GENERAL CONSIDERATIONS AND ANALYSIS POPULATIONS

This is a Phase 1, prospective, open label study to evaluate the safety, tolerability, and PK of EPN-701, administered once daily for 14 days in subjects with ESRD on a stable maintenance hemodialysis regimen. The primary objective of the study is to determine the safety and tolerability of EPN-701 (administered for two weeks at a daily dose of 10 mg).

There are no efficacy assessments or endpoints in this study. The primary (safety) endpoint is the frequency of treatment-emergent AEs and treatment-emergent AEs assessed as related to the study drug. Pharmacokinetic parameters and biomarkers represent secondary and/or exploratory endpoints.

The analysis populations are defined as follows:

- Safety population: all enrolled subjects who received at least one dose of study drug.
- PK population: all enrolled subjects who received at least one dose of study drug and have sufficient plasma concentrations data for PK analysis.

All analyses will be descriptive. Binary and categorical data will be summarized by number and percentage of subjects. Continuous data will be summarized by means, standard deviations (SDs), medians, and ranges (minimum, maximum), as appropriate.

All data will be included in appropriate per-subject listings.

Planned analyses are presented in the following sections.

11.2 DETERMINATION OF SAMPLE SIZE

No formal sample size calculation was performed. The selected sample size of 15 subjects is consistent with preliminary safety and PK studies of a similar design and is expected to provide sufficient information to identify safety issues, while limiting subject exposure.

11.3 SUMMARIES OF SUBJECT DISPOSITION

All enrolled subjects will be accounted for. The number of subjects who enroll, discontinue, or complete the study will be listed and summarized. All early treatment discontinuations and withdrawals from the study will be summarized by primary reason of discontinuation/withdrawal.

Time in trial and treatment exposure will also be summarized.

Protocol deviations and reasons for granting waivers (as applicable) will be categorized and provided in by-subject listings.

11.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables such as age, sex, race/ethnicity, and other relevant baseline characteristics will be summarized using means, SDs, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

The baseline value of any variable will be defined as the last available value prior to the first administration of the study drug.

11.5 EFFICACY ANALYSES

Not applicable.

11.6 SAFETY ANALYSES

Safety analyses will include all enrolled subjects who received at least one dose of the study drug (EPN-701).

Safety will be assessed through summaries of AEs, changes in safety laboratory test results, changes in vital signs, ECG parameters, and study drug exposures.

The primary safety endpoint is the frequency of treatment-emergent AEs (defined as any AE with an onset between the first dose of the study drug and the last study visit, or any AE with an onset prior to first dose that increases in severity or frequency after the first dose of study drug) and treatment-emergent AEs assessed as related to the study drug. Adverse events include both clinical events and laboratory abnormalities that are assessed as clinically significant.

Secondary safety endpoints include:

- Frequency of SAEs, AEs leading to study drug discontinuation, and AESIs
- Changes from baseline in safety laboratory parameters
- Changes from baseline in vital signs measurements
- Changes from baseline in ECG parameters.

11.6.1 Adverse Events

All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be included in per-subject listings. In addition, treatment-emergent AEs

(defined as any AE with an onset between the first dose of the study drug and the last study visit, or any AE with an onset prior to first dose that increases in severity or frequency after the first dose of study drug) will be summarized in frequency tables, by MedDRA System Organ Class (SOC) and by Preferred Term (PT), regardless of the investigator-determined relationship to study drug. For each subject, if there are multiple occurrences of the same AE, the maximum severity reported will be used in the summaries.

Adverse events assessed as related to the study drug will be summarized in a similar manner. A summary of AEs by maximum severity grade will also be provided.

The following treatment-emergent AEs will also be summarized:

- Adverse events leading to permanent discontinuation of study drug (with or without withdrawal from the study)
- Adverse events leading to dose interruption
- Serious adverse events
- AESIs
- Deaths.

11.6.2 Concomitant Medications

Concomitant Medications: All concomitant medications will be coded using the most current version of the World Health Organization (WHO) Drug Dictionary and will be included in per-subject listings.

11.6.3 Safety Laboratory Parameters

Laboratory parameters will be summarized at each time point measured using descriptive statistics, including means, SDs, medians, and ranges, as appropriate. Change from baseline will be summarized similarly, with 95% confidence intervals (CIs) for each change. Shift tables may also be provided, if warranted by the data. All safety laboratory data will be included in appropriate per-subject listings, along with reference ranges, and indication of clinically significant departures from the respective reference ranges.

Clinically significant laboratory abnormalities will be analyzed as part of the analysis of AEs.

11.6.4 ECG Changes and Abnormalities

ECG parameters: will be included in appropriate per-subject listings. In addition, a tabulated summary of the following parameters will be provided:

- number (%) of subjects with QT interval and QT interval corrected for heat rate using the Fridericia's formula (QTcF) >500 msec
- changes from baseline of >30 msec and of >60 msec in QT and QTcF values
- number (%) of subjects with clinically significant ECG abnormalities.

Clinically significant ECG abnormalities will be analyzed as part of the analysis of AEs.

11.7 PHARMACOKINETIC ANALYSES

The PK analyses will include all subjects who received at least one dose of study drug and have sufficient plasma concentrations data for PK analysis.

EPN-701 plasma concentration will be measured at specific timepoints (see **Table 1**), tabulated and summarized by assessment time point. Descriptive statistics for plasma concentrations and PK parameters will include arithmetic means and SDs, geometric means and coefficients of variation, medians, and ranges, as appropriate.

In addition, depending on the plasma concentrations observed at the pre-specified time-points, the following PK parameters may be summarized using the same descriptive statistics as for plasma concentrations:

- C_{max} [ng/mL]
- T_{max} [hr]
- AUC_{0-24} [hr×ng/mL].

11.8 BIOMARKER ANALYSES

Pre-defined biomarker endpoints include:

- Plasma levels of the following biomarkers on Day 15 (end-of-treatment) and Day 22 compared to baseline:
  - Uncarboxylated MGP
  - Uncarboxylated osteocalcin
  - Activated Protein C
  - PIVKA-II protein.

Exploratory biomarker endpoints include:

- Plasma levels of the following biomarkers on Day 15 (end-of-treatment) and Day 22 compared to baseline: osteoprotegerin, Fetuin A, *hs*-CRP, and Time to Formation of Secondary Calciprotein Particles (T-50 Test), including CPP size.

Biomarkers will be summarized in a similar manner as described for safety laboratory parameters, with a descriptive summary provided for each assessment time-point along with changes from baseline. Depending of the distribution of the biomarkers, transformations to minimize skew and outliers may be performed.

11.9 SUBGROUP ANALYSES

No subgroup analyses are planned.

11.10 INTERIM ANALYSIS

No interim analyses are planned.

A SRC will review the safety data accumulated during the study at regular intervals, as described in Section 10.6.

11.11 HANDLING OF MISSING DATA

To provide the best overview of this small study population, without introducing a possible unknown bias through imputation, all study data will be summarized as observed, with no imputation of missing values.

12. DATA COLLECTION AND MANAGEMENT

12.1 CASE REPORT FORMS

Subject data collected during the study will be recorded on eCRFs, which will be completed through use of a Sponsor-designated EDC system. Sites will undergo appropriate training and will receive a manual with instructions on adequate eCRF completion.

All eCRFs should be completed by designated, trained site staff, and should be reviewed and electronically signed and dated by the investigator. eCRFs will be submitted electronically (via the EDC system) to the Sponsor (or designee).

At the end of the study, the investigator will receive all subject data for his or her site in a readable format (e.g., on a compact disc) that must be kept with the study records.

12.2 DATA QUALITY ASSURANCE

Principles of quality control will be applied to each stage of data handling to ensure that all data are reliable and have been entered and processed correctly. Only qualified personnel will be allowed to enter data into the clinical database, which will have documented requirements for completeness, accuracy (including verification of the data), reliability, and consistent intended performance. Any changes to the data will be captured in a readable audit trail. Documentation will be kept indicating the individual tasks and the personnel authorized to perform them. The data will be checked for completeness, accuracy, and logic; any missing, illegible or illogical data will be queried. Responses to data queries will be entered following the same process as for the original eCRF. The investigator must review and approve all eCRF entries and responses to data queries.

Accurate and reliable data collection will also be assured by verification of the eCRF entries against the original source documentation, the drug dispensing log and study drug supplies by the study clinical research associate (CRA, also referred to as study monitor); refer to Section 12.3.

12.3 SITE MONITORING AND AUDITS

The investigator will permit Sponsor representatives, CRAs (study monitors), health authorities; and the reviewing IRB to inspect facilities and records relevant to this study, including direct

access to source data and documents, study drug and related accountability records, and the study-specific Site Master File (SMF).

Site visits will be conducted by the Sponsor or an authorized representative (CRA) at regular intervals throughout the study, for inspection of study data, subjects' medical records, eCRFs, and study drug supplies.

The Investigator must be available during the monitoring visits, as needed, and cooperate with the CRA to ensure that any problems detected during monitoring are promptly resolved.

12.3.1 Source Documentation

Source documents include, but are not limited to: clinic charts, dialysis flowsheets, subject files, hospital records, laboratory notes, subject-reported events and outcomes, ECG printouts, evaluation checklists and schedules, pharmacy dispensing records, data recorded from automated instruments, X-rays, microfilm, and records kept at pharmacies and laboratories involved in a clinical trial.

Source documents must not be obliterated or destroyed and must be retained for at least 15 years after completion or discontinuation of the study, or until at least 2 years after the last approval of a marketing application for the study drug, whichever is longer.

12.3.2 Source Data Verification

Study monitors will perform ongoing source data verification to confirm that critical protocol data entered in the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents. To facilitate source data verification, the investigator must provide the Sponsor and its designees direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits (as applicable), and inspection by the applicable health authorities and IRB.

12.4 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study (including eCRFs, ICFs, ECG, and laboratory test results, source documents, and study-specific SMF) and the distribution of study drug (such as study drug inventory and accountability records), must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or until at least 2 years after the last approval of a marketing application for the study drug, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

13. ETHICAL CONSIDERATIONS

13.1 REGULATORY COMPLIANCE

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and with US FDA regulations and applicable local, state, and federal laws. The study will also comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

13.2 INFORMED CONSENT

The study will be conducted in accordance with FDA Code of Federal Regulations (CFR) Title 21, Part 50, Subpart B-Informed Consent of Human Subjects and the applicable local IRB requirements.

The investigator must obtain written informed consent from each prospective subject or they legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study, and before any study-related procedures, assessments, treatments, or protocol-required changes in the subject's ongoing management can be made. The clinical records for each subject should document the informed consent process and that written informed consent was obtained prior to participation in the study.

The consent forms will be revised each time there are changes to study procedures or when new information becomes available that may affect the willingness of the subject to participate. The final revised IRB-approved consent form(s) must be provided to the Sponsor for health authority submission purposes.

Subjects participating in the study must be re-consented to the most current version of the consent form, according to the applicable local law and IRB policy. A copy of each signed consent form must be provided to the subject or the subject's legally authorized representative. All signed and dated consent forms must remain in each subject's study file or in the site file and must be available for verification by study monitors at any time.

Subject authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996 may be included in the consent form or a separate HIPAA Authorization Form may be utilized, as per the site policies.

13.3 INSTITUTIONAL REVIEW BOARD

The study will adhere to CFR Title 21, Part 56 (Institutional Review Boards).

This protocol, the consent form, and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent) as well as any advertising or compensation given to the subject, will be submitted by the investigator to the IRB, and must be reviewed and approved by the IRB before the study is initiated. The

investigator should obtain written documentation of the IRB approval, specifying the date on which the committee met and granted the approval.

The investigator must also submit any protocol amendments for IRB approval in accordance with local procedures and regulatory requirements. Additional documents submitted to the IRB will include (as applicable): written IND safety reports or other safety-related communications from the Sponsor, and reports on major protocol deviations. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with FDA requirements and the policies and procedures established by their IRB and archived in the site's study file.

13.4 SUBJECT CONFIDENTIALITY

All information obtained during the conduct of the study that relates to an individual subject will be regarded and handled as confidential. Each subject will be assigned a unique subject identification (ID) number at enrollment. Throughout the study, participating subjects will be referred to using their study ID number, and initials. Subject names or other personal identifiers are not included in data sets or any other documents that are transmitted to the Sponsor or CRO designee.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the reviewing IRB(s), as appropriate.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to subjects unless required by law.

14. STUDY DOCUMENTATION

14.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, ICFs, and documentation of IRB approval. In addition, at the end of the study, the investigator will receive the subject data, including an audit trail containing a complete record of all changes to data.

14.2 PROTOCOL AMENDMENTS

Protocol amendments may only be prepared and issued by the Sponsor. All protocol amendments will be submitted to the FDA and the IRB in accordance with applicable regulatory and IRB requirements, and approval must be obtained before implementation of any changes, except (1) changes necessary to eliminate an immediate hazard to subjects or (2) administrative changes (e.g., change in contact information).

14.3 PROTOCOL DEVIATIONS

The investigator should document each protocol deviation, along with an explanation. The investigator should promptly report any deviations that might have an impact on subject safety and/or data integrity to the Sponsor and to the IRB in accordance with the IRB policies and procedures.

The Sponsor will review each protocol deviation and assess whether any require reporting to the FDA (e.g. deviations representing a serious breach of Good Clinical Practice guidelines).

Requests to waive protocol eligibility criteria, will not be approved in this study. After the subject is enrolled, any protocol exemption request must be approved by the Sponsor/Medical Monitor before it can be implemented.

14.4 PUBLICATION POLICY

The Sponsor will comply with all requirements for publication of study results.

The investigator must agree to submit any manuscript or abstract related to the study to the Sponsor prior to submission for publication or presentation. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Any inventions and resulting patents or improvements originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor.

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16. APPENDIX 1 - DEFINITION AND CLASSIFICATION OF CHRONIC KIDNEY DISEASE (CKD)

Chronic Kidney Disease

Chronic Kidney Disease (CKD) is defined as abnormalities of kidney structure or function (defined as a glomerular filtration rate [GFR] <60 mL/min/1.73 m^2), present for ≥3 months, with implications for health (KDIGO, 2012). Criteria for CKD include are detailed in the following table.

Table A. Criteria for Chronic Kidney Disease (either of the following present for ≥3 months)

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

Source: The National Kidney Foundation (NKF) Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, 2012

Among patients with CKD, the stage of disease is determined based on the level of kidney function (with higher stages representing lower GFR levels), irrespective of diagnosis. The KDOQI classification of CKD is presented in **Table A**, and further elaborated in **Table B**.

Table B. GFR Categories in Chronic Kidney Disease

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Source: The National Kidney Foundation (NKF) Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, 2012

Note: GFR categories G1 through G5 correspond to previous stratification into Stages 1 through 5.

Source: NKF KDOQI Guidelines

Kidney failure

Kidney failure is defined as GFR <15 ml/min/1.73 m^2 (GFR category G5). Kidney failure leads to the commonly recognized symptoms of uremia. The need for treatment of chronic kidney failure with dialysis and/or kidney transplantation arises in 1% of patients with CKD (KDIGO, 2012).

End-stage renal disease

End-stage renal disease (ESRD) includes patients treated by dialysis or transplantation, irrespective of the level of GFR (KDOQI, 2002).

Note: The current KDIGO guidelines on CKD (KDIGO, 2012) do not include a definition of ESRD.