VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA

Clinical Study Protocol

Title:	A Phase 1, Single-arm, Open-label Study to Evaluate the Pharmacokinetics and Safety of Intravenous Difelikefalin in Adult Chinese Subjects on Haemodialysis
Clinical Protocol Number:	KOR-CHINA-101
Version Date:	15 July 2021
Version Number:	1.0
Prior Version/Amendments:	Not applicable
Investigational Drug	Difelikefalin (CR845)
Co-ordinating Investigator:	Professor Li Zuo
Sponsor Contact:	Milica Enoiu, PharmD, PhD
Sponsor Address:	Vifor Fresenius Medical Care Renal Pharma Ltd. Rechenstrasse 37 St. Gallen CH-9014 Switzerland

SIGNATURE PAGE

Declaration of Sponsor

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This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice as amended.

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Signature of Co-ordinating Investigator Professor Li Zuo Director, Department of Nephrology, Peking University People's Hospital Unit 10C, Ward Building 11 Xizhimennan Street, Xicheng District Beijing, 100044 China Telephone: +86 10 8832 4008	Date (day month year)

INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

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I have read the attached protocol as specified on this page and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice as amended, and applicable local regulations, and guidelines.

I agree to ensure that financial disclosure statements will be completed by:

- me (including, if applicable, my spouse (or legal partner) and dependent children)
- my Sub-investigators

before the start of the study and to report any changes that affect my financial disclosure status for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Vifor Pharma.

Signature by the Investigator on this Protocol Signature Page documents review, agreement, and approval of the requirements contained within this protocol.

Signature of Principal Investigator	Date (day month year)

Name, Title, Address, Telephone Number of Principal Investigator

SYNOPSIS

KOR-CHINA-101

Title:	A Phase 1, Single-arm, Open-label Study to Evaluate the Pharmacokinetics and Safety of Intravenous Difelikefalin in Adult Chinese Subjects on Haemodialysis
Short Title:	Pharmacokinetics(PK) of intravenous (IV) difelikefalin in Chinese subjects on haemodialysis (HD)
Study Product:	Difelikefalin (CR845)
Study Population:	Adult Chinese subjects on HD
Phase:	1
Sponsor:	Vifor Fresenius Medical Care Renal Pharma Ltd.
Protocol Number:	KOR-CHINA-101
Co-ordinating Investigator:	Professor Li Zuo, Peking University People's Hospital, Beijing, China
Objectives:	Primary Objective: • To evaluate the PK profile of a repeated (3 times weekly) dose of difelikefalin in Chinese HD subjects over a 1-week treatment period. Secondary Objective: • To evaluate the safety and tolerability of a repeated (3 times weekly) dose of difelikefalin in Chinese HD subjects over a 1-week treatment period.
Design:	This is a Phase 1, single-arm, open-label study to evaluate the safety, PK, and tolerability of a repeated (3 times weekly) dose of difelikefalin administered as IV bolus injections to adult Chinese HD subjects.
Duration:	Total study duration for a single subject is up to 5 weeks including a screening period of up to 3 weeks, a treatment period of 1 week, and a safety follow-up period of 1 week (1 week to 10 days). The duration of PK sampling is 12 days (starting from treatment Day 1).
Treatment:	Investigational Product: Difelikefalin solution (IV formulation) will be provided in 2 R glass vials with an extractable volume of 1 ml of difelikefalin at a concentration of 50 µg/ml in 0.04 M isotonic acetate buffer, pH 4.5. Dosage and Administration: Eligible subjects will be administered 0.5 µg/kg of difelikefalin as a single IV bolus 3 times, within 15 minutes post-dialysis for 1 week.
Inclusion Criteria:	Subjects are eligible to be included in the study only if all of the following inclusion criteria apply: 1. Appropriate written informed consent has been provided by subject or legally acceptable representative. Written informed consent must be provided before any study-specific procedures are performed, including screening procedures.

	2. Subjects have the ability to understand the requirements of the study, in the Investigator's opinion. 3. Chinese subjects aged ≥18 to 85 years (inclusive), at the time of consent. 4. End-stage renal disease (ESRD) subjects who have been on HD for at least 3 months before enrolment in the study and are currently on HD 3 times per week. Subjects with or without associated pruritus may be enrolled. 5. Subjects with a prescription dry body weight between 40 and 100 kg, inclusive. 6. If female, is not pregnant, or nursing. 7. If female: a. Is surgically sterile; or b. Has been amenorrhoeic for at least 1 year and is over the age of 55 years; or c. Has a negative serum pregnancy test within 7 days before first dose of investigational product, and agrees to use adequate contraceptive precautions (e.g., hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomised partner, or abstinence) from the time of informed consent until 7 days after the last dose of investigational product. Note: If the result from serum pregnancy testing at screening is indeterminate due to possible human chorionic gonadotropin elevation secondary to ESRD unrelated to pregnancy, a serum pregnancy re-test may be repeated prior to treatment Day 1 to establish if a negative result can be confirmed. 8. If male, agrees not to donate sperm from the first dose of investigational product administration (Day 1) until 7 days after last dosing, and agrees to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after the last dose of investigational product. Note: No restrictions are required for a vasectomised male, provided his vasectomy was performed ≥4 months prior to screening.
Exclusion Criteria:	1. Known to be non-compliant with HD treatments and deemed unlikely to complete the study by the Principal Investigator (i.e., has a history of missed HD sessions due to non-adherence in the past 2 months). 2. Planned or anticipated to receive a kidney transplant during the study. Note: Being listed on a kidney transplant list is not an exclusion criterion. 3. Known or suspected history of alcohol, narcotic, or other drug abuse, or dependence within 12 months prior to screening. 4. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) greater than 2.5 × the reference upper limit of normal (ULN), or bilirubin (total) greater than 4 × the ULN at screening. 5. Subjects with severe hepatic impairment (Child-Pugh Class C). 6. Acute or unstable medical condition(s) such as congestive heart failure (New York Heart Association Class IV), which in the opinion of the Investigator would pose undue risk to the subject or would impede complete collection of the data or its evaluability.

	7. Known history of allergic reaction to opiates such as hives. Note: Side effects related to the use of opioids such as constipation or nausea would not exclude the subjects from the study. 8. Subject has known hypersensitivity to the study intervention or any component of the investigational product formulation. 9. Subject has received another investigational drug within 30 days prior to the start of the screening visit or has planned to participate in another clinical trial while enrolled in this study.
Primary and Secondary Endpoints:	<u>Primary Endpoint</u>: • Evaluate the PK profile of difelikefalin, e.g., C_{max}, $T_{max,}$ area under the curve $(AUC)_{0\text{-}t}$, AUC_{inf}, $AUC_{extrap(\%),}$ $t_{½}$, clearance, and volume of distribution (V_z), when administered after each dialysis session (3 times a week) over a 1-week treatment period. <u>Secondary Endpoint</u>: • Overall safety and tolerability of difelikefalin as assessed by incidence of adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, and clinical safety laboratory evaluations over the study period.
Procedures:	See Table 1 for full details of protocol required assessments, procedures, and applicable visits (and timings of each visit). During the screening period, which may occur up to 21 days prior to the treatment period, following the signing of the informed consent, subjects are assessed for study eligibility. Eligible subjects will be admitted to the research unit clinic on Day -1. Dosing and PK assessments will begin on Day 1, which will be the first scheduled dialysis day of the week for the subject (i.e., either Monday, or Tuesday). Subjects must remain overnight in the research unit on the nights of Days -1, 1, 4, and 5 (i.e., domiciled continuously from Day -1 to middle of Day 2 and from Day 4 to middle of Day 6) at minimum and will be dialysed in the research unit on Days 1, 3, 5, 8, 10, and 12. Based on logistical considerations, subjects may also remain overnight in the research unit on the nights of Days 2 and 3 (i.e., domiciled continuously from Day -1 to middle of Day 6). The investigational product will be administered as an IV bolus within 15 minutes after the end of the dialysis session on Days 1, 3, and 5. The investigational product will be administered based on 0.5 µg/kg of dry body weight. The total dose volume (ml) required from the difelikefalin vial should be calculated as follows: 0.01 × prescription dry body weight (kg), rounded to the nearest tenth (0.1 ml). The investigational product may be given either during or after rinse back of the dialysis circuit. Following the IV push of investigational product, the venous line must be flushed with at least 10 ml of normal saline. PK samples will be collected on Days 1, 2, 3, 5, 6, 8, 10, and 12. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination. Vitals signs, physical examinations, 12-lead ECG, clinical laboratory tests will be monitored periodically, and AEs and concomitant medications will be continuously recorded during the study. A final safety follow-up visit will be conducted on Day 14 (up to +3 days).

Sample Size:	This study will enrol 30 subjects. The sample size for this Phase 1 study is based on a pragmatic approach. No formal sample size calculation has been conducted.
Study Sites:	1-4 study sites in China
Statistical Methods:	Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be finalised prior to database lock. Any deviation from the SAP will be noted and explained in the clinical study report. All individual data will be listed as measured. Frequency tables for categorical variables (absolutes and relative frequencies) and descriptive statistics for continuous variables (i.e., number of subjects, mean, standard deviation (SD), minimum, median, quartiles, and maximum) will be calculated. All statistical analyses will be purely descriptive. Analysis Populations: The following subject populations will be used for presentation and analysis of the data: • The safety analysis set (SAF) consists of all enrolled subjects who have received at least 1 dose of investigational product. • The PK population is defined as all subjects who have received the investigational product, did not have major protocol deviations or other events that may affect PK, and have sufficient plasma concentration. The PK population will be finalised prior to database lock. **Pharmacokinetics** All PK analyses will be performed using the PK analysis set. Noncompartmental PK analysis will be applied to derive all PK parameters in this study. Plasma difelikefalin concentrations will be summarised descriptively by nominal time at each time point. Individual and mean plasma concentration-time profiles and spaghetti plots (individual subject profiles in one plot) will be provided. In addition, individual plasma difelikefalin concentrations will be listed by subject. All PK parameters (e.g., C_{max}, T_{max}, AUC_{0-t}, AUC_{inf}, $AUC_{extrap(\%)}$, $t_{½}$, clearance, and V_z) will be summarised descriptively. Descriptive statistics will include N, mean (arithmetic and geometric), SD, median, coefficient of variation, minimum, quartiles, and maximum. **Safety** All safety analyses will be performed using the SAF. Incidence of AEs, adverse events of special interest (AESI), and serious adverse events (SAEs) will be tabulated by system organ class (SOC) and preferred term (PT), using Medical Dictionary for Regulatory Activities (MedDRA) coded terms. Incidence of AEs will also be summarised by maximum intensity and maximum relationship to the investigational product. Vital signs, biochemistry, haematology data, and 12-lead ECG recordings will be descriptively summarised by visit as applicable, in addition to change from baseline.

Figure 1 Study Design

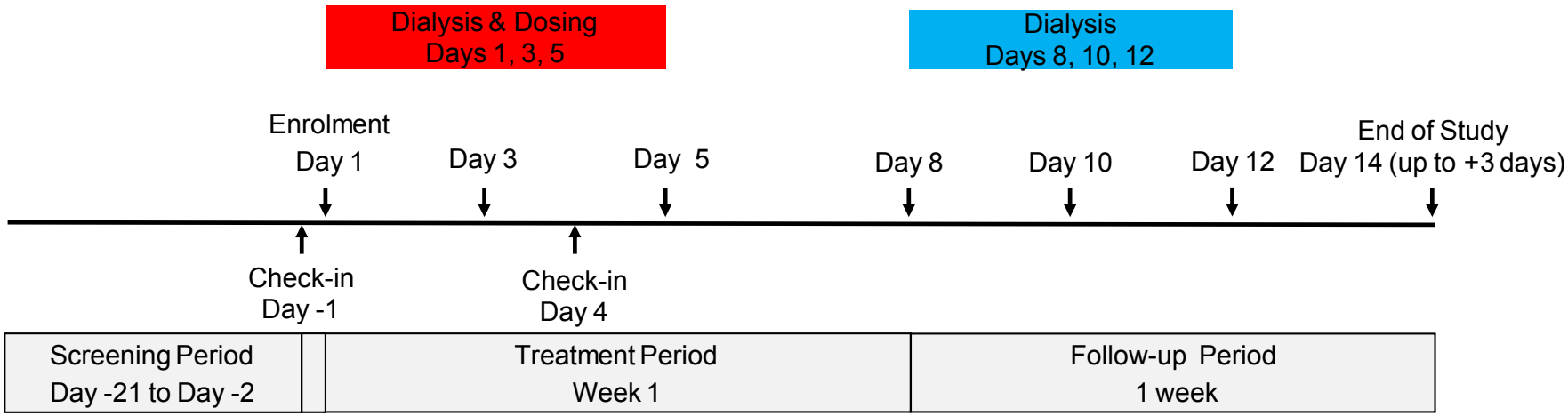

Table 1 Schedule of Events and Assessments

	Screening		Treatment Period								Follow-Up		
	Week -3 to -1		Week 1							Week 2	End of Study/ Early Termination		
	Day −21 to Day −2[1]	Day −1	Day 1 Pre-dose	Day 1 Post-dose	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 10	Day 12	Day 14 (+ up to 3 days)
Dialysis Day			M/Tu			W/Th		F/Sa		M/Tu	W/Th	F/Sa	
Informed consent	X												
Dispense subject identification card	X												
Eligibility criteria	X	X[2]											
Demographics	X												
Medical/surgical history	X	X[2]											
Admission to clinic within 24 hours before dialysis		X					X						
Overnight stay in clinic during night of visit[3]		X	X				X	X					
Dialysis[4]			X			X		X		X	X	X	
Investigational product administration (post-dialysis)[5]			X			X		X					
Blood sample(s) for PK (see Table 2)			X	X	X	X		X	X	X	X	X	
Physical examination	X	X[2]								X			
Height	X												
Prescription dry body weight	X		X										
12-lead ECG (pre-dialysis)	X[6]		X[7]							X[7]			
Pre-dialysis vital signs	X[6]		X[7]			X[7]		X[7]		X[7]			X[6]
Serum chemistry and haematology (pre-dialysis)[8]	X[6,9]		X[7]			X[7]		X[7]		X[7]			X[6]

	Screening		Treatment Period								Follow-Up		
	Week -3 to -1		Week 1							Week 2	End of Study/ Early Termination		
	Day −21 to Day −2[1]	Day −1	Day 1 Pre-dose	Day 1 Post-dose	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 10	Day 12	Day 14 (+ up to 3 days)
Dialysis Day			M/Tu			W/Th		F/Sa		M/Tu	W/Th	F/Sa	
Serum pregnancy[9]	X[10]												X[6]
AEs monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Visit at screening and at end of study/early termination should be on a dialysis day (for assessments to be performed pre-dialysis).
2 To be done either on Day −1 or on Day 1.
3 Based on logistical considerations, subjects may also remain overnight in the research unit on Days 2 and 3 (i.e., domiciled continuously from Day −1 to middle of Day 6).
4 The dialysis prescription should be kept constant throughout the study (See Section 9.7 for details).
5 Administration of investigational product takes place after dialysis (see Section 6.2 for details). Investigational product will be administered as an IV bolus into the venous line of the dialysis either during or after rinse back of the dialysis circuit, followed by flushing with at least 10 ml of normal saline. The actual dose of investigational product given (in ml) will be recorded in eCRF.
6 Obtain within 6 hours prior to starting dialysis, whenever possible.
7 Obtain within 2 hours prior to starting dialysis.
8 Serum chemistry: albumin, bilirubin (total), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, glucose, serum creatinine, blood urea nitrogen, electrolytes (sodium, potassium, chloride, calcium, and phosphorus). Haematology: haemoglobin, haematocrit, platelet count, white blood cell count (including differential).
9 Performed at central laboratory.
10 To be done in women of childbearing potential within 7 days prior to the first dose of investigational product.
Notes: AEs=Adverse events; ECG=Electrocardiogram; eCRF=Electronic Case Report Form; F=Friday; IV=Intravenous; M=Monday; PK=Pharmacokinetic; S=Saturday; Th=Thursday; Tu=Tuesday; W=Wednesday.

Table 2 Pharmacokinetic Samples Schedule

	Time After Drug Administration											
Study Day	**Pre-dialysis[1]**	**Post-dialysis[2]**	**5 min[3]**	**15 min[3]**	**30 min[3]**	**1 h[3]**	**2 h[3]**	**4 h[3]**	**6 h[3]**	**8 h[3]**	**12 h[3]**	**24 h[3]**
1	X	X	X	X	X	X	X	X	X	X	X	
2	–	–	–	–	–	–	–	–	–	–	–	X
3	X	X	–	–	–	–	–	–	–	–	–	–
5	X	X	X	X	X	X	X	X	X	X	X	–
6	–	–	–	–	–	–	–	–	–	–	–	X
8	X	X	–	–	–	–	–	–	–	–	–	–
10	X	X	–	–	–	–	–	–	–	–	–	–
12	X	X	–	–	–	–	–	–	–	–	–	–

1 Pre-dialysis blood samples will be taken at any time prior to the start of dialysis.
2 Blood samples will be taken at 5 minutes (±2 minutes) following the end of the dialysis.
3 Time is relative to the time of injection (i.e., t=0). A ±2-minutes window is allowed for pharmacokinetics blood draws up to 30 minutes (inclusive); a ±5-minutes window is allowed for the 1-hour to 8-hours blood draws and ±1 hour for the 12- and 24-hours blood draws.
Note: Pharmacokinetic samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination.

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CKD	chronic kidney disease
CKD-aP	chronic kidney disease-associated pruritus
C_{max}	maximum concentration
CNS	central nervous system
CRO	Contract Research Organisation
ECG	electrocardiogram
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	electronic data capture
ESRD	end-stage renal disease
EU	European Union
GCP	Good Clinical Practice
HD	haemodialysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IV	intravenous
KOR	kappa opioid receptor
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic

PT	preferred term
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
V_z	volume of distribution
WI-NRS	Worst Itching Intensity Numerical Rating Scale

1. INTRODUCTION AND BACKGROUND

Difelikefalin is a novel, selective kappa opioid receptor (KOR) agonist that is being developed as a therapeutic agent for the symptomatic relief of pruritus and pain.

Chronic kidney disease-associated pruritus (CKD-aP), also known as uraemic pruritus, is a distressful medical condition, common in >60% of chronic kidney disease (CKD) patients undergoing HD [1]. However, there are currently no approved treatments for CKD-aP in the US, Europe, or China. Difelikefalin is a KOR agonist with limited central nervous system (CNS) penetration that aims to fill this void by effectively and safely reducing itch in HD patients. At the time of this study protocol, difelikefalin has not been approved for marketing in any country.

1.1 Background of the Disease and Treatment Options

CKD-aP is characterised by a generalised and persisting itch, which has a negative impact on quality of life and is associated with depression, anxiety, sleep disturbance, and increased mortality. The incidence of CKD-aP is decreasing given advances in HD technology; however, approximately 42%, 21%, 11%, and 8% of HD patients in China, are somewhat bothered, moderately bothered, very much bothered, and extremely bothered by pruritus [1]. In a single-centre study in China described by Li et al, 2015, the prevalence of uraemic pruritus was reported to be 65.2% in continuous ambulatory peritoneal dialysis patients [2]. In another single-centre study conducted in China, Wen et al, 2020 reported that over 80% of HD patients were bothered by uraemic pruritus (among those bothered, 36-57% had moderate-to-severe pruritus) [3].

The pathophysiology of CKD-aP is not well understood; however, it is multifactorial and is attributed to imbalance of opioid receptors, uraemic toxins build-up, immune system dysregulation, systemic inflammation, peripheral neuropathy, hyperparathyroidism, etc [4,5].

Treatment of pruritus in HD patients depends on the severity of itching; treatment varies from use of topical therapy (emollients, steroid analgesics, local anaesthetics) in patients with mild or localised symptoms, to optimisation of dialysis parameters and systemic treatment in patients with more severe or generalised itching [6]. However, many patients have an inadequate response to existing treatments (topical or internal). Nalfurafine hydrochloride, an oral mixed nonselective mu partial agonist/KOR agonist, is effective in treating pruritus and is approved in Japan and South Korea for improvement of pruritus in HD patients; however, because of the oral formulation, HD patients have to take a large number of tablets, which increases the already high burden of these patients having to take many oral drugs. In addition, many HD patients have decreased salivary secretion and restricted fluid intake, and thus may have difficulty in taking the oral drug. Furthermore, as nalfurafine hydrochloride activates KOR in the CNS and in the gastrointestinal tract, this frequently induces adverse drug reactions (ADRs), such as sleep loss and constipation [7].

This creates the need to develop new treatments that are more convenient for use and cause fewer ADRs.

Opioid receptors are involved in the modulation of pain and itching signals and are subdivided into 3 subtypes, classified as mu, kappa, and delta. These receptor subtypes are found in the CNS (i.e., brain and spinal cord), on sensory ganglionic neurons and their nerve fibres innervating peripheral tissues such as skin, and on certain cell types of the immune system. The mu opioid receptor binds to β-endorphin, inhibits pain, and induces itching; KOR binds to dynorphin and inhibits pain and itching [8,9]. Morphine, the most widely clinically used opiate analgesic, acts primarily via activation of mu opioid receptors located in the CNS and peripheral nervous system. As such, it is associated with a wide array of side effects such as sedation, respiratory depression, abuse liability, constipation, cardiovascular collapse, and death. To avoid these undesirable effects, difelikefalin, a small, synthetic peptide KOR agonist, was designed; difelikefalin has a limited entry into the CNS, thereby predominantly activating KORs expressed on peripheral neurons and immune cells.

Difelikefalin has greater than 30,000-fold selectivity over human mu and delta opioid receptors, and no significant detectable activity at other receptors, ion channels, transporters, or enzymes. The selective activity of difelikefalin at KORs avoids the mu opioid receptor associated side effects characteristic of most opioid analgesics, such as respiratory depression, dependence, and euphoria [10,11].

Because of its physicochemical properties (i.e., hydrophilic) difelikefalin is expected to be safer and more tolerable; difelikefalin does not pass through the blood-brain barrier, which limits such undesirable CNS effects as activation of central KORs, i.e., dysphoria and psychomimetic effects [10]. In addition, difelikefalin is mostly renally excreted, resulting in a long half-life in HD patients ($t_{½}$ about 24 hours) and clearance by dialysis (see the latest difelikefalin Investigator's Brochure (IB)).

Furthermore, difelikefalin is expected to enhance the quality of pharmaceutical management that includes treatment compliance, treatment instructions, and remaining drug check because it is an injectable formulation administered directly from the dialysis circuit at the end of each dialysis session without fail under the supervision of a physician.

There are currently no marketed peptide KOR agonists in the US, the EU, or China.

1.2 Summary of Nonclinical and Clinical Data

1.2.1 Summary of Nonclinical Data

Provided here is a summary of the nonclinical data for difelikefalin. For more details, please refer to the latest version of difelikefalin IB.

- The physicochemical properties of difelikefalin (hydrophilic, synthetic D-amino acid peptide with high polar surface area and charge at physiological pH) minimise passive diffusion or active transport through the blood-brain barrier, thus limiting penetration into the brain. The limited to no brain exposure is further supported by radiolabelled studies and pharmacological studies suggesting that difelikefalin does not readily enter the CNS, and preferentially activates KORs located primarily in the peripheral nervous system and on immune cells.

- Nonclinical pharmacological studies indicate that difelikefalin has combined antipruritic, analgesic, and anti-inflammatory properties.

- Difelikefalin is primarily excreted unchanged into the urine and bile with no major metabolites identified. Nonclinical data indicate that difelikefalin should not significantly affect the clearance and/or metabolism of any co-administered drug(s).

- Generally, dose-proportional, linear PK in systemic exposure were observed following single IV or oral doses, with $t_{½}$ ranging from 1.1 to 5.5 hours. Similar kinetics were observed after repeated administration.

- No notable safety concerns after IV or oral administration of difelikefalin were identified in studies of acute and chronic toxicology (up to 6 months in the rat and 9 months in the monkey), safety pharmacology, reproductive and development toxicology, genotoxicity, and carcinogenicity.

1.2.2 Summary of Clinical Data

This will be the first Phase 1 clinical trial for evaluating PK, safety, and tolerability of difelikefalin in Chinese HD subjects. However, PK, safety, and efficacy of IV difelikefalin for the treatment of CKD-aP in HD patients have been previously investigated in multiple Phase 1, 2, and 3 clinical studies conducted outside of China (including 2 Phase 1 and 2 Phase 2 clinical studies in Japan).

Difelikefalin has been evaluated as either IV bolus or 15-minute infusion as single or repeated doses ranging from 0.25 to 40 μg/kg. In the clinical development program, IV difelikefalin has been administered to 3,478 subjects; 2,488 subjects have received IV formulation, and 990 have received oral formulation. A total of 1,592 CKD subjects on HD have received IV difelikefalin; of these, 1,096 subjects have received IV difelikefalin for at least 12 weeks; and 415 subjects with moderate-to-severe pruritus have received IV difelikefalin for at least 48 weeks.

Considering all the data relevant to the efficacy and safety of IV difelikefalin, the benefit/risk profile of difelikefalin in HD patients is considered favourable.

Provided below is a summary of the clinical data for difelikefalin. For more details, please refer to the latest version of difelikefalin IB.

1.2.2.1 Pharmacokinetics

In subjects with normal renal function, difelikefalin has linear and dose-proportional PK, with $t_{½}$ of approximately 2-3 hours after single dose IV administration. In subjects with CKD on HD, $t_{½}$ increases at least 10-fold compared with subjects with normal renal function.

Following single dose IV administration of (^{14}C)-difelikefalin to healthy volunteers or HD subjects, >99% of circulating plasma radioactivity remained as unchanged difelikefalin.

In both healthy volunteers and HD subjects, most of the dose excreted into urine and faeces was unchanged difelikefalin with minor quantities of putative metabolites, none exceeding 2.5%.

In a Japanese clinical pharmacology study in healthy subjects (Study PR-13A9-P1-A), the cumulative urinary excretion rate became almost constant by 36 hours after the initial dose (i.e., 15 hours after the final dose). The cumulative urinary excretion rate for up to 72 hours after the initial dose (i.e., 51 hours after the final dose) ranged from 71.6% to 76.8%, being similar across the dose groups (1.0, 3.0, 5.0, 10, 20, and 40 µg/kg).

In Japanese HD subjects (Study PR-13A9-P1-B), plasma difelikefalin concentrations after the first and third IV doses showed a biphasic elimination pattern of a rapid initial phase and a slow elimination phase. The $t_{½}$ of difelikefalin was 34.1 to 39.0 hours after the first dose and 40.0 to 49.3 hours after the third dose. The accumulation ratio of Day 5 to Day 1 calculated using the C_{max}, AUC_{0-48}, and trough values indicated a low likelihood of accumulation of difelikefalin.

1.2.2.2 Safety of IV Difelikefalin

In general, IV difelikefalin has been well tolerated in both single and repeat-dose clinical studies for up to 12 weeks at doses <5 µg/kg in healthy volunteers and subjects with CKD.

In subjects with normal renal function, IV difelikefalin produces a transient and generally dose-related increase in urine output without loss of electrolytes (0 to 12 hours after dosing). This aquaretic effect (i.e., free water loss) is a known pharmacological effect of KOR agonists and is managed with fluid replacement, as applicable.

In healthy volunteers exposed to IV difelikefalin, the most common treatment-emergent adverse events (TEAEs) (≥5.0% of subjects) with an incidence ≥1.0% greater compared with placebo were, in descending frequency, paraesthesia, hypoaesthesia, dizziness, sedation, headache, and fatigue. There was an apparent dose-response relationship with difelikefalin for the majority of TEAEs, with the highest incidence observed at IV difelikefalin doses >5 µg/kg. There was 1 reported SAE of sinus tachycardia in a difelikefalin-treated subject and none in placebo-treated subjects. No specific TEAEs leading to investigational product discontinuation occurred in >1 subject.

In subjects with CKD on HD exposed to IV difelikefalin, the most common TEAEs (≥5.0% of subjects) with an incidence ≥1.0% greater compared with placebo were, in descending frequency, diarrhoea, nausea, insomnia, fall, hypotension, abdominal pain, dizziness, vomiting, hyperkalaemia, headache, pneumonia, and dyspnoea. The most common SAEs (≥1.0% of subjects) among difelikefalin-treated subjects with an incidence ≥1.0% greater compared with placebo were, in descending frequency, pneumonia, fluid overload, sepsis, hyperkalaemia, respiratory failure, mental status changes, acute myocardial infarction, gastrointestinal haemorrhage, syncope, asthenia, and non-cardiac chest pain. Observed SAEs were consistent with underlying medical conditions in the subject population. The most common TEAEs leading to investigational product discontinuation among difelikefalin-treated subjects were cardiac arrest, somnolence, and dizziness.

In a Japanese Phase 1 clinical study (Study PR-13A9-P2-A, healthy volunteers), blood sodium increased was reported in 4/6 subjects in the 5.0 µg/kg group during the repeated-dose period. These events were reported only in clinical studies in subjects with normal renal function and have not been reported in clinical studies in HD subjects.

In a Japanese Phase 2 clinical study (Study MR13A9-3, JapicCTI-163265, n=84 subjects on HD), common TEAEs (reported in ≥10% of subjects) included blood thyroid stimulating hormone decreased, dizziness, blood prolactin increased, nausea, feeling abnormal, and somnolence. Study treatment was discontinued or interrupted due to 1 event in 1 subject in the 0.25 µg/kg group, 2 events in 2 subjects in the 0.5 µg/kg group, 1 event in 1 subject in the 1.0 µg/kg group, and 17 events in 10 subjects in the 1.5 µg/kg group. Dependency was assessed as being present in 2 subjects in the placebo group and 1 subject in the 0.5 µg/kg difelikefalin group.

In a Japanese Phase 2 clinical study (Study MR13A9-4, NCT03802617, n=184 subjects on HD), common TEAEs (reported in ≥3% of subjects) included somnolence, dizziness, palpitations, vomiting, nausea, and blood thyroid stimulating hormone decreased. Study treatment was discontinued or interrupted due to 5 events in 4/61 subjects in the 0.5 µg/kg group and 6 events in 5/62 subjects in the 1.0 µg/kg group. Dependency was assessed as being absent in all evaluable subjects.

1.2.2.3 Efficacy of IV Difelikefalin

The efficacy of IV difelikefalin in reducing itch-related quality of life in subjects with CKD on HD has been demonstrated in Phase 2 and Phase 3 clinical studies.

- In a Phase 2 study CR845-CLIN2101 [12], the efficacy outcomes were similar across the 0.5, 1, and 1.5 µg/kg dose groups after each HD (i.e., 3 times a week; 8 weeks of treatment); with statistically significant differences favouring difelikefalin over placebo most often observed in the 0.5 µg/kg dose group. Together with the more favourable safety profile seen in the 0.5 µg/kg group, the 0.5 µg/kg dose group was selected for evaluation in Phase 3 studies (12 weeks of treatment).

- In a Japanese Phase 2 clinical study (MR13A9-3), 105 CKD-aP subjects on HD received IV difelikefalin (0.25, 0.5, 1.0, or 1.5 µg/kg), or placebo 3 times weekly for 2 weeks. The primary endpoint of change in visual analogue scale (i.e., change based on the larger visual analogue scale value either in the morning or the evening during the 7 days, the latter half of the treatment period) suggested a dose-dependent improvement by treatment with difelikefalin at doses ≥0.5 µg/kg.

- In a Japanese Phase 2 clinical study (MR13A9-4), 247 CKD-aP subjects on HD received IV difelikefalin (0.25, 0.5, or 1.0 µg/kg, or placebo 3 times weekly for 8 weeks). The primary variable of change from baseline in the mean Numerical Rating Scale score at Week 8 of the treatment period (adjusted mean ± standard error) was −2.97±0.29 in the difelikefalin 0.25 µg/kg group, −3.65±0.30 in the 0.5 µg/kg group, and −3.64±0.30 in the 1.0 µg/kg group, compared with −2.86±0.29 in the placebo group. These results showed significant improvement in the difelikefalin 0.5 and 1.0 µg/kg groups compared with the placebo group, indicating a dose-response relationship showing a constant effect at doses of ≥0.5 µg/kg.

- In the first Phase 3 double-blind, randomised, placebo-controlled, parallel group US study (CR845-CLIN3102) [13] in subjects with CKD on HD with moderate-to-severe pruritus, IV bolus administration of difelikefalin 0.5 µg/kg after each HD (i.e., 3 times a week) for 12 weeks resulted in a significant effect, with a higher proportion of subjects treated with difelikefalin showing ≥3-point (least squares (LS) mean of 51.0% of difelikefalin subjects versus 27.6% of placebo subjects, $p<0.001$) and ≥4-point (LS mean of 38.9% of difelikefalin subjects versus 18.0% of placebo subjects, $p<0.001$) reductions in Worst Itching Intensity Numerical Rating Scale (WI-NRS) score at Week 12; the reduction in the severity of itch intensity was observed within 1 week of treatment. Significant improvements in itch-related quality of life were observed in this study.

- In the second Phase 3 double-blind, randomised, placebo-controlled, parallel group global study (CR845-CLIN3103) in subjects with CKD on HD with moderate-to-severe pruritus, IV bolus administration of difelikefalin 0.5 µg/kg after each HD (i.e., 3 times a week) for 12 weeks resulted in a significant effect, with a higher proportion of subjects treated with difelikefalin showing ≥3-point (LS mean of 54.0% of difelikefalin subjects versus 42.2% of placebo subjects, $p=0.020$) and ≥4-point (LS mean of 41.2% of difelikefalin subjects versus 28.4% of placebo subjects, $p=0.010$) reductions in WI-NRS score at Week 12; the reduction in the severity of itch intensity was observed within 2 weeks of treatment. Improvements in itch-related quality of life were also observed in this global study.

- In a Phase 3, 12-week, open-label study (CR845-CLIN3105) in subjects with CKD on HD with moderate-to-severe pruritus, difelikefalin 0.5 μg/kg IV resulted in a reduction in pruritus, as measured by the percentage of subjects with a ≥3-point (73.7%) and ≥4-point (59.3%) improvement in WI-NRS score. Improvements in itch-related quality of life were also observed.

2. RATIONALE

2.1 Patient Need

The number of patients in China undergoing HD is increasing each year [14]. Approximately 42% of HD patients in China, are distressed by moderate or severe pruritus [1]. The benefits of the KOR agonist difelikefalin in reducing itch in CKD-aP patients undergoing HD has been demonstrated in multiple Phase 2 and Phase 3 clinical studies outside of China. Currently, in China, there are no approved KOR agonists for the treatment of itch in subjects with CKD on HD. Study KOR-CHINA-101 will be the first clinical trial with IV difelikefalin in subjects on HD to be conducted in China.

Clinical data outside of China have shown the benefits of difelikefalin in patients undergoing HD; IV difelikefalin was well tolerated with an acceptable safety profile in CKD-aP patients undergoing HD.

Considering all the data relevant to the efficacy and safety of IV difelikefalin, the benefit/risk profile of the product in subjects with CKD-aP is considered favourable.

2.2 Study Design

This study is designed to evaluate the PK, safety, and tolerability of 0.5 µg/kg IV difelikefalin in Chinese subjects with ESRD on HD (3 times weekly) with or without associated pruritus. A dialysis frequency of 3 times a week (versus twice weekly), is prevalent for the dialysis practice in China [14].

The eligibility criteria for the present study will provide a cohort of Chinese subjects who have ESRD and are undergoing HD (and may have or not CKD-aP). In these subjects, HD is often associated with pruritus, and subjects will benefit from an investigational product that reduces the intensity of pruritus.

This study design (e.g., dose, investigational product administration, time points for PK sampling) is based on previous clinical trials with difelikefalin in CKD subjects on HD conducted by Cara Therapeutics, Inc. previously outside of China (including clinical trials conducted in Japan by licensees of Cara Therapeutics, Inc.).

The PK and safety parameters are standard for the assessment of these aspects of an investigational product. Considering the PK profile of difelikefalin—limited membrane permeability, metabolically stable, and primarily excreted unchanged in the urine—difelikefalin PK in Chinese subjects is expected to be similar to the PK data obtained in clinical trials outside of China.

IV administration of difelikefalin will occur at the end of HD by using the return HD line or via injection directly into a vein. In order to avoid the contamination of PK samples with difelikefalin, PK samples are to be collected from a different venous access than the site used for investigational product administration.

2.3 Dose Selection

The dose to be evaluated in this study, a single dose of 0.5 μg/kg difelikefalin (administered 3 times weekly), is based on results of clinical studies conducted outside of China. The dose of 0.5 μg/kg IV difelikefalin was shown to be effective and with a favourable safety profile in global studies and in clinical studies in Japan. A lower dose (0.25 μg/kg) did not show efficacy in a Phase 2 study in Japan (M13A9-4); a higher dose (1 μg/kg) was shown to be effective in Western subjects and in Japanese subjects; however, the incidence of AEs also increased in a dose-dependent manner.

The efficacy of 0.5 μg/kg IV difelikefalin in CKD subjects has been confirmed in 2 pivotal, Phase 3, randomised 12-week placebo-controlled studies, demonstrating statistically significant and clinically relevant reductions in pruritus. The treatment effect started as early as 1 week after initiating treatment, and the benefit was maintained for at least 1 year in the long-term extensions of these studies. No unexpected safety signals emerged during a long-term treatment of up to 52 weeks with 0.5 μg/kg IV difelikefalin, with the nature and rate of the reported safety events aligning with published morbidity and mortality data of patients with CKD-aP undergoing HD.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

- To evaluate the PK profile of a repeated (3 times weekly) dose of difelikefalin in Chinese HD subjects over a 1-week treatment period.

3.2 Secondary Objectives

- To evaluate the safety and tolerability of a repeated (3 times weekly) dose of difelikefalin in Chinese HD subjects over a 1-week treatment period.

3.3 Primary Endpoint

- To evaluate the PK profile of difelikefalin, e.g., C_{max}, $T_{max,}$ $AUC_{0\text{-}t}$, AUC_{inf}, $AUC_{extrap(\%)}$, $t_{½}$, clearance, and V_z, when administered after each dialysis session (3 times a week) over a 1-week treatment period.

3.4 Secondary Endpoint

- Overall safety and tolerability of difelikefalin as assessed by incidence of AEs, vital signs, 12-lead ECG, and clinical safety laboratory evaluations over the study period.

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 1, single-arm, uncontrolled, open-label study to evaluate the PK, safety, and tolerability of a repeated (3 times weekly) dose of difelikefalin administered as IV bolus injections to adult Chinese HD subjects (Figure 1).

Subjects eligible for the study will receive a unique subject number. Enrolled subjects who terminate their study participation for any reason regardless of whether the investigational product was administered or not, will retain their number. The next subject will be given the next unique subject number.

Enrolled subjects will be administered 0.5 µg/kg of difelikefalin as a single IV bolus 3 times, within 15 minutes post-dialysis for 1 week. The first dose will be administered on Day 1. The first HD will be the first scheduled dialysis day of the calendar week for the subject (i.e., Monday, or Tuesday).

The schedule of assessments is provided in Table 1.

4.2 Duration of Subject Participation and Study

The expected duration of subject participation is a maximum of 5 weeks: screening period duration is up to 3 weeks; treatment period duration is 1 week; and follow-up period is 1 week (1 week to 10 days).

The end of study is defined as the last subject last visit.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects

This study will enrol 30 subjects. The sample size for this Phase 1 study is based on a pragmatic approach. No formal sample size calculation has been conducted.

5.2 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria apply:

1. Appropriate written informed consent has been provided by subject or legally acceptable representative. Written informed consent must be provided before any study-specific procedures are performed, including screening procedures.

2. Subjects have the ability to understand the requirements of the study, in the Investigator's opinion.

3. Chinese subjects aged ≥18 to 85 years (inclusive), at the time of consent.

4. End-stage renal disease (ESRD) subjects who have been on HD for at least 3 months before enrolment in the study and are currently on HD 3 times per week. Subjects with or without associated pruritus may be enrolled.

5. Subjects with a prescription dry body weight between 40 and 100 kg, inclusive.

6. If female, is not pregnant, or nursing.

7. If female:

    a. Is surgically sterile; or

    b. Has been amenorrhoeic for at least 1 year and is over the age of 55 years; or

    c. Has a negative serum pregnancy test within 7 days before first dose of investigational product, and agrees to use adequate contraceptive precautions (e.g., hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomised partner, or abstinence) from the time of informed consent until 7 days after the last dose of investigational product. Note: If the result from serum pregnancy testing at screening is indeterminate due to possible human chorionic gonadotropin elevation secondary to ESRD unrelated to pregnancy, a serum pregnancy re-test may be repeated prior to treatment Day 1 to establish if a negative result can be confirmed.

8. If male, agrees not to donate sperm from the first dose of investigational product administration (Day 1) until 7 days after last dosing, and agrees to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after the last dose of investigational product. Note: No restrictions are required for a vasectomised male, provided his vasectomy was performed ≥4 months prior to screening.

5.3 Exclusion Criteria

The following criteria exclude a subject from participating in this trial:

1. Known to be non-compliant with HD treatments and deemed unlikely to complete the study by the Principal Investigator (i.e., has a history of missed HD sessions due to non-adherence in the past 2 months).

2. Planned or anticipated to receive a kidney transplant during the study. Note: Being listed on a kidney transplant list is not an exclusion criterion.

3. Known or suspected history of alcohol, narcotic, or other drug abuse, or dependence within 12 months prior to screening.

4. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) greater than 2.5 × the reference upper limit of normal (ULN), or bilirubin (total) greater than 4 × the ULN at screening.

5. Subjects with severe hepatic impairment (Child-Pugh Class C).

6. Acute or unstable medical condition(s) such as congestive heart failure (New York Heart Association Class IV), which in the opinion of the Investigator would pose undue risk to the subject or would impede complete collection of the data or its evaluability.

7. Known history of allergic reaction to opiates such as hives. Note: Side effects related to the use of opioids such as constipation or nausea would not exclude the subjects from the study.

8. Subject has known hypersensitivity to the study intervention or any component of the investigational product formulation.

9. Subject has received another investigational drug within 30 days prior to the start of the screening visit or has planned to participate in another clinical trial while enrolled in this study.

5.4 Withdrawal of Subjects

5.4.1 Withdrawal of Subjects from the Study

Subjects may voluntarily withdraw from study participation at any time without having to provide a reason. Subjects may be withdrawn because of the appearance of a new health

condition requiring care or medications prohibited by the protocol, unacceptable AEs, refusal to continue treatment, major non-compliance with study procedures, significant protocol deviations, or at the Investigator's discretion if it is in the subject's best interest.

If a subject withdraws from the study at any time either at his or her request or at the Investigator's discretion, the reason(s) for withdrawal must be recorded on the relevant page of the subject's eCRF and source documentation. Subjects who withdraw from the study prematurely should undergo all end of study assessments, if possible.

If a subject is withdrawn from the study due to an AE, it is vital to obtain follow-up data. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures (see Section 10.3). If a subject is discontinued due to an AE, the event should be followed by the Investigator through contact with the subject until resolution or stabilisation has occurred. All AEs should be followed until resolution, stabilisation, or the subject is lost to follow-up and cannot be contacted.

If a subject refuses to continue study procedures, the reason for refusal should be fully documented in the subject's source document and recorded in the study-specific eCRF. Although subjects are not obliged to give a reason for withdrawing consent, the Investigator should make every effort to obtain the reason, while fully respecting the subject's rights. If the subject withdraws from the trial without providing a reason, the source documents and the eCRF should document the reason for discontinuation as "withdrawal by subject".

Subjects who discontinue from the study after administration of the first dose of investigational product and before completing the protocol procedures will not be replaced.

6. STUDY TREATMENTS

6.1 Dosage Forms/Formulation

The investigational product used in this study has been manufactured in accordance with current Good Manufacturing Practice.

Investigational product (IV formulation) will be provided in 2 R glass vials with an extractable volume of 1 ml of difelikefalin at a concentration of 50 µg/ml in 0.04 M isotonic acetate buffer, pH 4.5. Investigational product will be provided by the Sponsor for this study.

Active Ingredient:	Difelikefalin
Chemical Name:	4-amino-1-((R)-6-amino-2-((R)-2-((R)-2-((R)-2-amino-3-phenylpropanamido)-3-phenylpropanamido)-4-methylpentanamido)hexanoyl)piperidine-4-carboxylic acid
Abbreviated Peptide Sequence:	D-phenylalanyl-D-phenylalanyl-D-leucyl-D-lysyl-γ-(4-N-piperidinyl)-amino-carboxylic acid, acetate salt
Strength:	0.05 mg (free base)/ml
Excipients:	0.04 M isotonic acetate buffer, pH 4.5
Appearance:	Clear, colourless solution
Dosage Form:	Injection
Manufacturer:	Siegfried Hameln GmbH
Storage:	Do not freeze

6.2 Investigational Product Dosage and Administration

The investigational product will be dispensed by qualified staff members who have received training on investigational product handling and administration.

Individual IV doses of investigational product are based on subject body weight (0.5 µg/kg dry body weight) and prepared by withdrawing subject-specific volume of investigational product with sterile, single-use 1 ml Plastipak syringe (or equivalent) and sterile single-use needles. A single vial cannot be used for multiple subjects. Vials contain an extractable volume of 1 ml of investigational product.

The total dose volume (ml) required from the vial should be calculated as follows: 0.01 × prescription dry body weight (kg), rounded to the nearest tenth (0.1 ml). The total dose volumes per weight range are detailed in Table 3.

Table 3 Total Dose Volumes per Weight Range

Weight Range (Dry Body Weight in kg)		Dose (ml)
40	44	0.4
45	54	0.5
55	64	0.6
65	74	0.7
75	84	0.8
85	94	0.9
95	100	1.0

If the syringes are prepared using aseptic techniques, subjects must be dosed (IV bolus) within 24 hours of syringe preparation with capped syringes stored at 2°C to 8°C until use. If the syringes are not prepared using aseptic techniques (i.e., prepared under a sterile hood), subjects must be dosed within 60 minutes of syringe preparation. If the syringes are used within 60 minutes of preparation, they do not need to be kept refrigerated. No other special procedures are required for the safe handling of the solutions.

Difelikefalin will be administered by IV bolus injection within 15 minutes following the end of the dialysis on the scheduled investigational product administration day. Difelikefalin may be given either during or after rinse back of the dialysis circuit. Difelikefalin administration can be done by injection into the dialysis venous line (e.g., into the venous port) or by direct injection into a vein. If the dialysis line is used, following the bolus, the venous line must be flushed with at least 10 ml of normal saline. The actual dose of difelikefalin administered (in ml) will be recorded in the eCRF.

Additional details on dose preparation and administration will be provided in the Pharmacy Manual.

6.3 Package and Labelling

The investigational product will be packaged and labelled in accordance with local regulations for investigational products.

6.4 Study Treatment Allocation

This is an open-label study. All subjects will receive difelikefalin.

6.5 Site Supply, Storage, Accountability

6.5.1 Site Supply

Once a site has been approved to receive investigational product, the site will be supplied with an initial stock of investigational product used in the study. The need for drug resupply will be assessed on a regular basis considering the number of subjects enrolled, and the number of subjects in screening at the site.

6.5.2 Storage

The investigational product must be stored at 15º to 25ºC. Each site should have a thermometer that records minimum and maximum temperatures daily. Maintenance of a temperature log is mandatory. The log should be updated by site personnel every workday. This log must be available for review by the Monitor during on-site monitoring visits.

Additional information on storage of the investigational product including prepared dosing syringes is provided in the Pharmacy Manual.

6.5.3 Accountability

The Investigator at each site is responsible for investigational product supplies. The Investigator will ensure that adequate records of the receipt, preparation, administration and return of the investigational product are kept and that the investigational product is used only for subjects enrolled in the study. All data regarding the investigational product (including kit and batch numbers) must be recorded in the eCRF and on any other relevant forms provided.

Each study site will maintain a drug inventory/dispensing record for all drugs dispensed and returned. At the end of the study, 1 copy of the drug inventory/dispensing record should be sent to the Sponsor for the central study file. The original will be kept in the site files.

After completion of the study, or if it is prematurely terminated, all unused materials will be returned to the Sponsor. The decision to destroy investigational product at site must first be made by the Sponsor. If the investigational product is destroyed at site, the Investigator will forward the certificate of destruction to the Sponsor.

6.6 Drug Dose Modification

Dose modifications are not allowed in this study.

6.6.1 Procedures for Overdose

There is no information available on the effect of overdosing with difelikefalin. In an attempt to reverse this condition, an opioid antagonist such as naloxone may be considered for acute management of IV overdose although the clinical effectiveness of naloxone to antagonise the effects of difelikefalin has not been confirmed in humans. In extreme cases, dialysis may be considered for the treatment of overdose.

Any occurrence of an overdose must be communicated to the Medical Monitor and the Sponsor (see Section 10.8).

6.7 Concomitant Treatment

Any concomitant treatment (including traditional Chinese medicines) given for any reason during the study must be recorded on the eCRF and in the subject's medical records, including dosage, start and stop dates and reason for use.

All prescription and non-prescription medications (e.g., over-the-counter drugs and herbal supplements) that subjects report taking during the 30 calendar days prior to the screening visit will be recorded in the eCRF as prior medications.

All drugs and therapies used after the Informed Consent Form (ICF) was signed should be recorded in the eCRF as concomitant medications.

For each medication, documentation should list the trade or generic name, the total daily dose including units (or the dose, units, and scheduled and actual frequency of administration if the medication is not taken daily), the route of administration, and the reason for use.

Changes, additions, or discontinuations to medications will be assessed and recorded in the eCRF during each study visit. All as needed prescriptions should be converted to reflect actual dose taken per day.

Any medication or therapy that is taken by or administered to the subject during the study must be recorded in the eCRF.

COVID-19 vaccination during study participation will be recorded as concomitant medications. Based on the mechanism of action of difelikefalin, an interaction with the COVID-19 vaccinate or an impact of the vaccination on difelikefalin PK are unlikely. Moreover, the administration of investigational product 3 times a week for 1 week as well as the short duration of samples collection for PK limit the impact of the COVID-19 vaccination on the study.

7. RISKS/PRECAUTIONS

7.1 Risks

In clinical studies, IV difelikefalin has been administered to 1,096 CKD subjects on HD for at least 12 weeks (3 months); of these subjects, 415 CKD subjects on HD with moderate-to-severe pruritus have been exposed to IV difelikefalin for at least 48 weeks (12 months).

The most common (≥5.0% of subjects) adverse effects to difelikefalin reported from clinical studies in subjects with CKD on HD with an incidence ≥1.0% greater compared with placebo were, in descending frequency, diarrhoea, nausea, insomnia, fall, hypotension, abdominal pain, dizziness, vomiting, hyperkalaemia, headache, pneumonia, and dyspnoea.

Somnolence (including MedDRA PTs of somnolence and sedation) and mental status changes (including MedDRA PTs of mental status changes and confusional state) have been reported as serious ADRs, with frequencies of 0.12% and 0.17%, respectively, in subjects being treated with difelikefalin during clinical developmental (including the indication for treating pruritus; N=3,478).

7.2 Precautions

Aquaresis is defined as the increase in urinary water excretion with the sparing of electrolytes, which can result in dehydration, hypotension, tachycardia, and increases in serum sodium.

Aquaresis may be observed in subjects with normal renal function. The increases in serum sodium in difelikefalin-treated subjects with normal renal function have been generally dose-related, transient, and clinically asymptomatic.

In CKD subjects on HD, the aquaretic effects of difelikefalin do not apply due to insufficient functioning of nephrons.

7.2.1 Drug Interactions

The nonclinical data suggest that difelikefalin should possess minimal to no drug-drug interaction potential in humans. However, the effects of other drugs on difelikefalin kinetic parameters have not been evaluated.

7.2.2 Drug Abuse and Dependency

Difelikefalin has been shown to have a low to no risk to induce drug-seeking behaviour in humans. Based on clinical data including dedicated physical dependence studies conducted in humans and rodents, it can be concluded that difelikefalin has very low to no physical dependence potential.

7.2.3 Hypersensitivity

Difelikefalin is contraindicated in subjects with hypersensitivity to KOR agonists or any component of difelikefalin formulation.

7.2.4 Women of Childbearing Potential

Women of childbearing potential can only be enrolled in the study if:

- They are surgically sterile
- Have been amenorrhoeic for at least 1 year and are over the age of 55 years
- Have a negative serum pregnancy test within 7 days before first dose of investigational product, and agree to use adequate contraceptive precautions (e.g., hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomised partner, or abstinence) from the time of informed consent until 7 days after dosing

  Note: If the result from serum pregnancy testing at screening is indeterminate due to possible human chorionic gonadotropin elevation secondary to ESRD unrelated to pregnancy, a serum pregnancy re-test may be repeated prior to treatment Day 1 to establish if a negative result can be confirmed.

7.2.5 Pregnancy and Lactation

Safety and efficacy of difelikefalin have not been established in pregnant women. Although difelikefalin does not affect embryonic development in animal models, pregnant women cannot be enrolled in this study.

Safety and efficacy of difelikefalin have not been established in nursing mothers. Animal data indicate that difelikefalin is secreted into breast milk. Therefore, difelikefalin may only be administered after breastfeeding is discontinued and nursing mothers cannot be enrolled in this study.

8. STUDY ASSESSMENTS AND PROCEDURES

For a detailed schedule of assessments and procedures (including all protocol required assessments, visits and visit windows) please refer to Table 1.

8.1 Allowed Adaptations in Case of Extraordinary Events, e.g., COVID-19

The guidance below is intended for subjects who have been successfully enrolled into the study and who are unable to attend in person clinic visits due to COVID-19 restrictions. Every reasonable effort should be made to ensure that the subject continues on the study per-protocol. Study visits which coincide with dialysis days should be conducted on-site. In the event that a subject cannot come to the clinic after baseline visit due to self-quarantine, local restrictions, or illness, a visit at another local hospital may be considered.

If the subject misses, or is expected to miss, 2 consecutive clinic visits due to COVID-19, the Investigator must contact the Medical Monitor to discuss discontinuation of the subject from the study. In either scenario, the subject should return to the clinic for assessment at their earliest convenience. If it is determined that the subject must be discontinued, the reason for termination should be documented as 'related to COVID-19' under Reason for Termination: Other in the eCRF.

Extraordinary events may call for specific measures to maintain subject safety and guarantee conduct of clinical investigations according to established general and specific guidelines and regulations to meet agreed regulatory, quality, and scientific expectations.

For this, the following adaptations are considered for specific situations:

- Site visits are not possible within the defined time window, possibly leading to delayed visit:
  - On-site monitoring: accept delayed on-site monitoring, conduct remote monitoring.
  - On-site auditing: accept delayed on-site auditing, conduct remote auditing.
  - AE/SAE/special situation reporting: frequent phone call visits.
- Site visits are not possible within the defined time window, possibly leading to no visit:
  - Vital signs: consultation by local physician, follow-up clinical assessment via phone remote visits at subject's home (e.g., home nursing).
  - On-site monitoring: accept delayed on-site monitoring, conduct remote monitoring.
  - On-site auditing: accept delayed on-site auditing, conduct remote auditing.

- AE/SAE/special situation reporting: frequent phone call visits.

8.2 Screening Procedures (Day -21 to Day -2)

The screening visit is to occur within 21 calendar days prior to the start of treatment; it should be on a dialysis day (for assessments to be performed pre-dialysis).

After the subject has signed the ICF, the following assessments will be performed and recorded in the subject's source documentation/medical record and on the eCRF:

- Assign subject number and dispense subject identification card
- Eligibility criteria
- Demographics
- Medical/surgical history
- Physical examination
- Height and prescription dry body weight
- 12-lead ECG (pre-dialysis) obtained within 6 hours prior to starting dialysis, whenever possible
- Pre-dialysis vital signs obtained within 6 hours prior to starting dialysis, whenever possible
- Serum chemistry obtained within 6 hours before starting dialysis, whenever possible (central laboratory assessment)
  - Albumin, bilirubin (total), alkaline phosphatase (AP), ALT, AST, glucose, serum creatinine, blood urea nitrogen (BUN)
  - Electrolytes (sodium, potassium, chloride, calcium, and phosphorus)
- Haematology obtained within 6 hours before starting dialysis, whenever possible (central laboratory assessment)
  - Haemoglobin, haematocrit, platelet count, white blood cell count (including differential)
- Serum pregnancy in women of childbearing potential (central laboratory assessment) to be done within 7 days prior to the first administration of investigational product
- AEs assessment

- Concomitant medications

8.3 Day −1

The following assessments and procedures will be performed 1 day before start of the investigational product administration:

- Confirmation of eligibility criteria
- Update medical/surgical history, if needed
- Admission to clinic 24 hours before dialysis
- Subject stays overnight in clinic during night of visit
- Physical examination, any time prior to the first dose (may also be done at Day 1)
- AEs assessment
- Concomitant medications

8.3.1 Day 1

The following assessments and procedures will be performed:

- Confirmation of eligibility criteria (if not done at Day −1)
- Update medical/surgical history (if needed and not done at Day –1)
- Physical examination (if not done at Day –1)
- Prescription dry body weight

Overnight stay in clinic during night of visit (based on logistical considerations, subjects may also remain overnight in the research unit on Days 2 and 3)

- 12-lead ECG to be obtained within 2 hours prior to starting dialysis
- Assess vital signs within 2 hours prior to starting dialysis
- Serum chemistry obtained within 2 hours before starting dialysis (local laboratory assessment)
  - Albumin, bilirubin (total), AP, ALT, AST, glucose, serum creatinine, BUN
  - Electrolytes (sodium, potassium, chloride, calcium, and phosphorus)

- Haematology obtained within 2 hours before starting dialysis (local laboratory assessment)
  - Haemoglobin, haematocrit, platelet count, white blood cell count (including differential)
- Pre-dialysis blood sample for PK can be taken at any time before starting dialysis
- Dialysis (first dialysis session of the study, i.e., Monday for subjects on a Monday-Wednesday-Friday dialysis schedule or Tuesday for subjects on a Tuesday-Thursday-Saturday dialysis schedule)
- Post-dialysis blood sample for PK will be taken at 5 minutes (±2 minutes) following the end of the dialysis. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination
- Within 15 minutes after dialysis, administer investigational product as an IV bolus into the venous line of the dialysis either during or after rinse back of the dialysis circuit, followed by flushing with at least 10 ml of normal saline
- Post-dose blood samples for PK as listed in Table 2. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination
- AEs assessment
- Concomitant medications

8.3.2 Day 2

- AEs assessment
- Concomitant medications
- Blood samples for PK at 24 hours (±1 hour) post-dose (investigational product administered on the previous day −Day 1). PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination.

8.3.3 Day 3

The following procedures and assessments will be performed:

- Pre-dialysis blood samples for PK (can be taken at any time before starting dialysis). PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination

- Assess vital signs within 2 hours before starting dialysis
- Serum chemistry obtained within 2 hours before starting dialysis (local laboratory assessment)
  - Albumin, bilirubin (total), AP, ALT, AST, glucose, serum creatinine, BUN
  - Electrolytes (sodium, potassium, chloride, calcium, and phosphorus)
- Haematology obtained within 2 hours before starting dialysis(local laboratory assessment)
  - Haemoglobin, haematocrit, platelet count, white blood cell count (including differential)
- AEs assessment
- Concomitant medications
- Dialysis (second dialysis session of the study, i.e., Wednesday for subjects on a Monday-Wednesday-Friday dialysis schedule or Thursday for subjects on a Tuesday-Thursday-Saturday dialysis schedule)
- Post-dialysis blood samples will be taken at 5 minutes (±2 minutes) following the end of the dialysis. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination
- Within 15 minutes after dialysis, administer investigational product as an IV bolus into the venous line of the dialysis either during or after rinse back of the dialysis circuit, followed by flushing with at least 10 ml of normal saline

8.3.4 Day 4

The following procedures and assessments will be performed:

- Admission to clinic 24 hours before dialysis
- Overnight stay in clinic during night of visit
- AEs assessment
- Concomitant medications

8.3.5 Day 5

The following procedures and assessments will be performed:

- Overnight stay in clinic during night of visit

- AEs assessment
- Concomitant medications
- Pre-dialysis blood sample for PK to be taken at any time before starting dialysis. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination
- Assess vital signs within 2 hours prior to starting dialysis
- Serum chemistry obtained within 2 hours before starting dialysis (local laboratory assessment).
  - Albumin, bilirubin (total), AP, ALT, AST, glucose, serum creatinine, BUN
  - Electrolytes (sodium, potassium, chloride, calcium, and phosphorus)
- Haematology obtained within 2 hours before starting dialysis (local laboratory assessment)
  - Haemoglobin, haematocrit, platelet count, white blood cell count (including differential)
- Dialysis (Friday for subjects on a Monday-Wednesday-Friday dialysis schedule or Saturday for subjects on a Tuesday-Thursday-Saturday dialysis schedule)
- Post-dialysis blood samples for PK will be taken at 5 minutes (±2 minutes) following the end of the dialysis. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination
- Within 15 minutes after dialysis, administer investigational product as an IV bolus into the venous line of the dialysis either during or after rinse back of the dialysis circuit, followed by flushing with at least 10 ml of normal saline
- Post-dose blood samples for PK as listed in Table 2. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination

8.3.6 Day 6

The following procedures and assessments will be performed:

- AEs assessment
- Concomitant medications

- Blood samples for PK at 24 hours (±1 hour) post-dose (investigational product administered on the previous day, Day 5). PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination

8.3.7 Day 8

The following procedures and assessments will be performed:

- AEs assessment
- Concomitant medications
- Physical examination
- 12-lead ECG to be obtained within 2 hours prior to starting dialysis
- Assess vital signs within 2 hours prior to starting dialysis
- Serum chemistry obtained within 2 hours before starting dialysis (local laboratory assessment)
  - Albumin, bilirubin (total), AP, ALT, AST, glucose, serum creatinine, BUN
  - Electrolytes (sodium, potassium, chloride, calcium, and phosphorus)
- Haematology obtained within 2 hours before starting dialysis (local laboratory assessment)
  - Haemoglobin, haematocrit, platelet count, white blood cell count (including differential)
- Pre-dialysis blood sample for PK to be taken at any time before starting dialysis. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination
- Dialysis (Friday for subjects on a Monday-Wednesday-Friday dialysis schedule or Saturday for subjects on a Tuesday-Thursday-Saturday dialysis schedule)
- Post-dialysis blood samples for PK will be taken at 5 minutes (±2 minutes) following the end of the dialysis. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination

8.4 Follow-up Procedures

8.4.1 Day 10

- Pre-dialysis blood sample for PK can be taken at any time before starting dialysis. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination

- Dialysis

- Post-dialysis blood sample for PK will be taken at 5 minutes (±2 minutes) following the end of the dialysis. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination

- AEs assessment

- Concomitant medications

8.4.2 Day 12

- Pre-dialysis blood sample for PK can be taken at any time before starting dialysis. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination

- Dialysis

- Post-dialysis blood sample for PK will be taken at 5 minutes (±2 minutes) following the end of the dialysis. PK samples are to be obtained from a venous access different from the site used for difelikefalin administration to avoid cross contamination

- AEs assessment

- Concomitant medications

8.4.3 End of Study (or Early Discontinuation) Procedures/Day 14 (+ up to 3 Days)

On completion of the study (i.e., Day 14 plus up to 3 days), or if subject is discontinued/withdrawn early, a last study visit should be conducted (on a dialysis day) and the following assessments and procedures should be performed:

- Assess vital signs within 6 hours prior to starting dialysis, whenever possible

- Serum chemistry obtained within 6 hours before starting dialysis, whenever possible (local laboratory assessment)

  – Albumin, bilirubin (total), AP, ALT, AST, glucose, serum creatinine, BUN

  - Electrolytes (sodium, potassium, chloride, calcium, and phosphorus)

- Serum pregnancy in women of childbearing potential (central laboratory assessment) to be done within 6 hours prior to starting dialysis, whenever possible

- Haematology obtained within 6 hours before starting dialysis, whenever possible (local laboratory assessment)

  - Haemoglobin, haematocrit, platelet count, white blood cell count (including differential)

- AEs assessment

- Concomitant medications

9. STUDY ASSESSMENTS

All assessments will be performed as noted in the Schedule of Events (Table 1).

9.1 Demographics and Medical/Surgical History

Subject's demographics (gender, age, race, and ethnicity) and baseline characteristics including prescription dry body weight, and medical history will be taken during the screening visit.

Information to be collected will include the aetiology and clinical presentation of CKD and CKD-related events (e.g., pruritus, CKD-mineral and bone disorder, secondary hyperparathyroidism), and the date when CKD was first diagnosed, and other clinically relevant past and present medical conditions which were diagnosed/occurred prior to signing the informed consent and/or for which the subject is currently treated. Any history of alcohol, narcotic, or other drug abuse or dependence within 12 months prior to screening will be collected.

All medications and treatments prescribed at the time of informed consent must be documented on the appropriate eCRF pages. In addition, treatments prescribed up to at least 3 months prior to obtaining the informed consent must be documented on the appropriate eCRF pages, irrespective if the treatment is still ongoing at the time of screening. All changes to or addition of concomitant treatments as of informed consent must be recorded (including changes in dose, change in formulation, starting or stopping medications) in the eCRF. If the indication for changing a subject's concomitant treatment constitutes a new medical condition or a worsening of an existing clinical condition which is considered by the Investigator as being clinically relevant, the indication must be documented as an AE (see Section 10).

Also, the date of the last HD will be recorded in the eCRF.

9.2 Physical Examination, Height, Vital Signs

Physical examination will include general appearance, cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes, and skin. Any findings before first administration of investigational product should be reported in the medical history. Clinically significant findings after first administration of study drug should be reported as AEs.

Height without shoes will be recorded in centimetres.

Vital signs will include body temperature (°C), respiratory rate, radial pulse rate, systolic and diastolic blood pressures. Sitting recordings are to be made after the subject has been sitting for at least 5 minutes with their feet squarely on the floor and arms relaxed, bent at the elbow.

An AE form must be completed for all changes identified as clinically noteworthy.

9.3 12-lead ECG

Standard 12-lead ECGs will be measured after the subject has been resting for minimum of 5 minutes.

All 12-lead ECG recordings (including heart rate, QT, QTcF, QTcB, RR interval, P-wave, QRS complex duration, and PR interval) will be performed and interpreted at study sites by Investigators. ECGs will be planned to coincide with first dialysis of the week. If this is not possible, ECGs should be planned for the same session of the week.

At screening, the Investigator must document clinically relevant ECG findings on the appropriate baseline eCRF pages. Any new clinically relevant ECG finding, or aggravation/worsening of an already existing finding as assessed by the Investigator, must be reported as an AE (see Section 10).

9.4 Clinical Laboratory Tests

The following clinical laboratory tests are to be performed as indicated in the Schedule of Events (Table 1).

- Serum chemistry (central laboratory assessment at screening, local laboratory assessments at subsequent visits)
  - Albumin, bilirubin (total), AP, ALT, AST, glucose, serum creatinine, BUN
  - Electrolytes (sodium, potassium, chloride, calcium, and phosphorus)
- Haematology obtained (central laboratory assessment at screening, local laboratory assessments at subsequent visits)
  - Haemoglobin, haematocrit, platelet count, white blood cell count (including differential)
- Other:
  - Serum pregnancy test in women of childbearing potential (central laboratory assessment)

Details on the processing and shipment of specimens are provided in the Laboratory Manual. In the event of an unexplained clinically noteworthy abnormal laboratory test value, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

Details on the clinical laboratories used in this clinical trial, such as address, accreditation certificates, are available in the Trial Master File.

9.5 Adverse Events

See Section 10.

9.6 PK Assessments

PK samples will be obtained from a venous access different from the site of difelikefalin administration to avoid cross contamination. Samples will be obtained at timepoints as noted in Table 1 and Table 2, within the allowed time windows. The exact time of PK samples collection must be recorded.

Details of the procedures to be followed for sample collection, storage, and shipment will be documented in a separate Laboratory Manual.

These samples will not be used to assess biomarkers or genetic markers.

9.7 Dialysis

The HD prescription should be kept constant throughout the study. If the dialysis prescription must be changed or if there is an access problem that precludes achieving the prescribed blood flows, please contact the Medical Monitor. Record procedural data (start and stop times, net ultrafiltration, access changes).

10. EVALUATION, RECORDING, AND REPORTING OF AEs

10.1 Definition of AEs

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the investigational product.

10.2 AE Reporting Period

The AE reporting period begins at the time the ICF is signed by the subject. The AE reporting period ends at the last study visit (end of study/early termination). For SAE reporting period, see Section 10.7.2.

10.3 Eliciting AEs

If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality. This may require additional laboratory testing, physical examinations, telephone contacts, etc.

In order to avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as "How are you feeling?" It is also important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be assessed as AEs.

10.4 Assessing AEs

10.4.1 Intensity/Severity

The medical assessment of intensity will be determined by using the following definitions:

Mild: The AE is easily tolerated and does not interfere with usual activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating, and the subject is unable to work or complete usual activity.

Every change in intensity of a particular AE experienced by the subject during the course of the event is recorded.

It is important to note the distinctions between severe AEs and SAEs. Severity is a classification of intensity of a specific event (as in mild, moderate, or severe myocardial infarction); however, the event itself may be of relatively minor medical significance (such

as severe headache). An SAE, however, is an AE that meets any of the regulatory specified criteria required for designation as seriousness described in Section 10.7.1, i.e., a headache may be severe (interferes significantly with subject's usual function but would not be classified as serious unless it met 1 of the criteria for SAEs).

10.4.2 Causality and Reporting

An Investigator who is qualified in medicine must make the determination of relationship to investigational product for each AE and SAE. The Investigator should decide whether, in her/his medical judgement, 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, then the AE/SAE should be classified as unrelated or unlikely related and an alternative suspected aetiology should be provided if available (i.e., concomitant medications, intercurrent illness/events). Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a cause-and-effect relationship between the investigational product and the occurrence of the AE/SAE, then the AE/SAE should be considered certainly, probably/likely, or possibly related.

The following additional guidance may be helpful:

Term	Relationship	Definition
Certain	Yes	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary.
Probable/ Likely	Yes	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required.
Possible	Yes	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear.
Unlikely	No	• Event or laboratory test abnormality with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanation.
Unrelated	No	• Event or laboratory test abnormality which is clearly related to circumstances not connected with the drug intake.

If the causal relationship between an AE/SAE and the investigational product is determined to be “certainly, probably/likely, or possibly related”, the event will be considered to be

related to the investigational product for the purposes of expedited regulatory reporting. In circumstances where the causal relationship has not been provided, the event will be considered as related and qualify for expedited regulatory reporting.

10.4.3 Outcome Categorisation

Outcome may be classified as: recovered/resolved (i.e., without sequelae); recovered/resolved with sequelae; recovering/resolving; not recovered/not resolved; fatal; or unknown (if follow-up is not possible).

If the outcome of an SAE is reported as recovered/resolved with sequelae, the Investigator should specify the kind of sequelae on the SAE form. If the outcome of an SAE is reported as unknown, the Investigator should specify (on the SAE form) the rationale why unknown was selected.

“Fatal” should be recorded as an outcome when the AE results in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for the AE that, in the opinion of the Investigator, is the most plausible cause of death. All other ongoing AE/SAEs will be recorded as not recovered/not resolved at the time of death.

In case of a fatal outcome, the Investigator should provide a working diagnosis (event which caused outcome, e.g., death due to fatal myocardial infarction) instead of reporting only death; and an autopsy report should be provided where possible. If the cause of death later becomes available (e.g., after autopsy), this working diagnosis should be replaced by the established cause of death.

Although “fatal” is usually an outcome of an event, events such as sudden death or unexplained death should be reported as SAEs.

10.5 Recording and Reporting

10.5.1 Persistent or Recurrent AEs

AEs that extend continuously, without resolution, between trial assessments should only be recorded once in the eCRF.

The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens.

AEs that resolve and subsequently recur should have each recurrence recorded separately in the eCRF.

All AEs persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilisation, or the subject is lost to follow-up and cannot be contacted. The outcome must be documented in the subject’s source documents.

10.5.2 Diagnosis Versus Signs and Symptoms

Where possible, the Investigator should report a diagnosis rather than individual signs and symptoms or abnormal laboratory values. However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

The Investigator should use standard medical terminology/concepts; avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in each event field in the eCRF.

10.5.3 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the medical history eCRF. A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

10.5.4 Clinical Laboratory Evaluations

Not every out-of-range laboratory result qualifies as an AE. A laboratory investigation result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalaemia) or a change in concomitant therapy
- Presents shift of a parameter from a normal value to a pathological value, or results in a deterioration of common terminology criteria grade, or a further worsening of an already pathological value
- Is clinically significant in the Investigator’s judgement

It is the Investigator’s responsibility to review all laboratory findings. Medical and scientific judgement should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product,

and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are pathological laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE. If the Investigator considers such an AE as serious (e.g., medically significant event fulfilling criteria per Section 10.7.1), it must be reported as an SAE.

If a laboratory abnormality meeting the above criteria is a sign of a disease or syndrome only the diagnosis should be recorded in the eCRF.

If a laboratory abnormality meeting the above criteria is not a sign of a disease or syndrome, the abnormality itself should be recorded in the eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., “elevated potassium,” as opposed to “abnormal potassium”).

If the laboratory abnormality can be characterised by a precise clinical term per standard definitions, the clinical term should be recorded as the AE, for example, hypercalcaemia or hypoglycaemia. Observations of the same laboratory abnormality from visit to visit should not be repeatedly recorded in the eCRF unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

All pathological laboratory findings/values diagnosed throughout the treatment period should be reviewed by the Investigator to provide a final clinical assessment in view of the dynamic of laboratory changes/abnormalities.

10.5.5 Worsening of the Disease Under Study

Symptoms and signs of the disease under study should not be considered AEs as long as they are not regarded as worsening of the clinical features of the disease under study. If a sign or symptom of the disease has unexpectedly worsened in severity or frequency or changed in nature at any time during the study, the symptoms and signs should be recorded as AEs, and clearly marked as worsening of the signs or symptoms in the eCRF.

10.5.6 Abnormal Vital Signs and Other Abnormalities

Not every abnormal vital sign, ECG, or other safety assessment qualifies as an AE. A result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms or lead to a diagnosis (in such case the symptom or diagnosis will be recorded as an AE)

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention, a change in concomitant therapy, or subject referral for further testing outside the protocol

- Clinically significant abnormality in the Investigator's judgement

It is the Investigator's responsibility to review all vital signs, ECG, and other safety findings. Medical and scientific judgement should be exercised in deciding whether an isolated abnormality should be classified as an AE.

If a clinically significant abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the eCRF.

Observations of the same clinically significant abnormality from visit to visit should not be repeatedly recorded in the eCRF unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

10.6 ADR and Reference Safety Information

10.6.1 Adverse Drug Reaction

An ADR is a response to a medical product (any dose administered). A causal relationship between an investigational product and an AE is at least a reasonable possibility. This means that there are facts (evidence) or arguments to suggest a causal relationship.

All AEs judged as having a reasonable causal relationship to an investigational product will be designated as ADRs.

10.6.2 Reference Safety Information

The Reference Safety Information presents the basis for expectedness assessment of an adverse reaction for expedited reporting and annual safety reporting, as well as surveillance of subject's safety in a clinical trial by regulatory (and ethic) bodies.

In the context of this study, the Reference Safety Information is integrated in the latest version of difelikefalin IB.

10.7 Serious Adverse Event

10.7.1 Definition of SAE

An SAE is defined as any untoward medical occurrence that either:

- Results in death

- Is life-threatening (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)

- Requires inpatient hospitalisation or prolongation of existing hospitalisation (unless elective surgery (a planned, non-emergency medical procedure))

- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect

- Is an important medical event (i.e., medically significant)

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events should also be considered as serious.

Any worsening of a pre-existing medical condition or any new medical condition that meets the above SAE criteria should be considered as an SAE.

Any suspected transmission of any infectious agent via a medicinal product should be considered as an important medical event (i.e., medically significant) and therefore documented as an SAE.

The Investigator is encouraged to discuss with the Sponsor (or its delegate, e.g., Contract Research Organisation (CRO)) any AEs for which the issue of seriousness is unclear or questionable.

10.7.1.1 Situations that are Not Considered SAEs

The following situations are not considered as SAEs:

- Visits to the emergency room or hospital department that do not result in a hospital admission lasting more than 24 hours

- Elective or pre-planned surgery for a pre-existing condition that has not worsened

- Routine health assessments requiring admission not associated with any deterioration in condition

- Social admission (lack of housing, family circumstances, etc.)

- A planned overnight stay for logistical reasons only prior to investigational product administration does not fulfil the criteria of an SAE unless there is also a medical reason for the admission

10.7.2 SAE Reporting

The SAE reporting period begins at the time the ICF is signed by the subject. The SAE reporting period ends 30 days following the last study visit or until 30 days after last investigational product administration, whichever is longer. After last study visit, SAEs that comes to the attention of the Investigator must be reported to the CRO/Sponsor and will be documented in the safety database of the Sponsor only and not in eCRF.

A death occurring during the study, or which comes to the attention of the Investigator within 30 days after the last study visit or until 30 days after the last investigational product administration, whichever is longer, whether considered treatment-related or not, must be reported to the Sponsor (or its delegate, e.g., CRO).

Any SAE considered to have a causal relationship (i.e., related) to the investigational product and discovered by the Investigator at any time after the study should be reported. A rationale for the assessment of a causal relationship must be provided by the Investigator. Any safety information that is obtained after database lock of the clinical database will be documented in the safety database and implications for handling the data in the clinical database assessed on an individual case basis.

The occurrence of an SAE must be immediately reported to the Sponsor (or its delegate, e.g., CRO) within 24 hours of awareness using the study-specific Sponsor SAE form/via SAE CRF/eCRF in the electronic data capture (EDC), or as defined in the study monitoring plan. This includes all SAEs (independent of relationship to study treatment).

The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious (i.e., met at least 1 of the criteria for seriousness; see Section 10.7.1). If the condition started as a non-serious event and then became serious, 1 AE and 1 SAE will be recorded. The resolution date of the SAE is defined as when the symptoms resolve, or the event is considered chronic (e.g., sequelae) or stable, and/or if the seriousness criteria are no longer applicable.

10.7.3 Suspected Unexpected Serious Adverse Reaction

The definition of a suspected unexpected serious adverse reaction is any ADR (see Section 10.6.1) that is both serious (see Section 10.7.1) and unexpected (per the Reference Safety Information; see Section 10.6.2) that, based on the opinion of the Investigator or Sponsor, is felt to have a reasonable possibility or suspected causal relationship to an investigational product.

10.7.3.1 SAE Expedited Reporting

The Sponsor will notify all Investigators of all SAEs requiring expedited reporting to Regulatory Authorities.

The Investigator is responsible for notifying the Independent Ethics Committee (IEC) in accordance with local regulations of all SAEs that occur. The Investigator must review and file the safety report with the IB.

10.8 Special Situations

10.8.1 Definition of Special Situations

The following are defined as special situations:

- Use of an investigational product during pregnancy or breastfeeding
- Use of an investigational product in a paediatric population
- Medication error: any unintentional error in the prescribing, dispensing or administration of an investigational product during the study
- Medication misuse: an intentional and inappropriate use of an investigational product not in accordance with the protocol dose, route of administration, and/or the indication(s)
- Medication overdose: the administration of a quantity of investigational product given per administration, which is above the protocol maximum permitted dose
- Drug interaction involving investigational product
- Unexpected therapeutic or clinical benefit from investigational product use

Suspected AEs associated with medication errors of the investigational product or use outside that foreseen in the protocol (e.g., overdose,) are also considered as ADRs. Any special situation occurring with/without ADR/AE shall be recorded in the study-specific documentation.

10.8.2 Special Situation Recording and Reporting

All special situations have to be documented in the subject's eCRF and source documents. The Investigator should also complete and submit the Sponsor paper Special Situation form immediately (i.e., within 24 hours of awareness) to the Sponsor, following the same procedure as for SAEs (Section 10.7.2).

If any special situation leads to an SAE (see Section 10.8.1), then the event must be immediately reported to the Sponsor (or its delegate, e.g., CRO) within 24 hours of awareness using the study-specific Sponsor SAE form/via SAE CRF/eCRF in EDC.

10.8.3 Pregnancy Exposure and Birth Events

10.8.3.1 Definition of Pregnancy Exposure and Birth Events

When a female subject becomes pregnant during the study and study treatment has been administered to the subject, the outcome of the pregnancy needs to be monitored and the safety of the mother and unborn child need to be safeguarded (as per-protocol, pregnancy is an exclusion criteria). Therefore, the outcome of all such pregnancies (including normal births) must be followed up and documented, even if the subject was withdrawn from the study or the study has been completed.

Women of childbearing potential, defined as a premenopausal female capable of becoming pregnant, should have a negative serum pregnancy test within 7 days before first dose of investigational product is administered and at the end of study treatment (Day 8). Investigational product should not be initiated by the Investigator until a report of a negative pregnancy test has been obtained. As per inclusion criteria, women of childbearing potential must agree to use adequate contraceptive precautions (e.g., hormonal contraceptives, barrier with spermicide, intrauterine device, vasectomised partner, or abstinence) from the time of informed consent until 7 days after dosing. Please also refer to the eligibility criteria (Section 5).

Per inclusion criteria, male subjects will agree not to donate sperm from investigational product administration until 7 days after the dosing and will agree to use a condom with spermicide or abstain from heterosexual intercourse during the study until 7 days after investigational product administration.

A female subject must immediately inform the Investigator if she becomes pregnant during the study and be instructed to stop taking investigational product. The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The Investigator/Sponsor is responsible for monitoring the subject and pregnancy outcome. Every effort should be made to gather information regarding the pregnancy outcome until 90 days postpartum (or otherwise as appropriate). It will be the responsibility of the Sponsor, together with the appropriate support of the Investigator, to obtain this information.

10.8.3.2 Pregnancy Exposure and Birth Events Recording and Reporting

Any report of pregnancy recorded for any female subject or for a female partner of a male subject should be reported to the Sponsor (or its delegate, e.g., CRO) within the same timelines as an SAE, i.e., immediately (within 24 hours of awareness). The outcome of all such pregnancies (including normal births) must be followed up and documented, even if the subject was discontinued from the study. Complications of pregnancy such as abortion (spontaneous or induced), premature birth (before 37 weeks gestational age) or congenital abnormality are considered SAEs and should be reported using the study-specific Sponsor SAE form.

All pregnancies occurring in a female subject or the female partner of a male subject within 90 days after discontinuation of the investigational product should be reported within the same timelines as a SAE to the Sponsor (or its delegate, e.g., CRO).

10.8.4 Adverse Event of Special Interest

10.8.4.1 Definition of AESI

An AESI is a medical occurrence specific to the product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate. Such an event, depending on the nature and the outcome, may be serious (see Section 10.7.1) or non-serious.

Based upon results of the studies in the HD population, the following categories (MedDRA PT) were identified as AESIs for the HD population:

- Gait disturbance (gait disturbance)
- Falls (fall)
- Dizziness (dizziness)
- Somnolence (somnolence)
- Seizures (seizure)
- Syncope (syncope)
- Mental status changes (mental status changes)
- Mood changes (mood altered)
- Unusual feeling/sensation (feeling abnormal)
- Tachycardia (sinus tachycardia, tachycardia, and tachyarrhythmia)
- Palpitations (palpitations)

10.8.4.2 AESI Reporting and Recording

AEs classified as AESIs will be noted in the AE section of the subject's eCRF and source documentation. Any AESI satisfying any of the criteria for seriousness should be reported using the study-specific Sponsor SAE form/via SAE CRF/eCRF in EDC. The Investigator should notify the Sponsor immediately (i.e., within 24 hours of awareness), following the same procedure as for SAEs (Section 10.7.2).

11. DATA AND SAFETY MONITORING BOARD/DATA MONITORING COMMITTEE PROCEDURES

An independent Data and Safety Monitoring Board/Data Monitoring Committee will not be used in this open-label study, whose primary objective is to evaluate the PK profile of a single dose (3 times weekly) of difelikefalin in Chinese subjects undergoing HD.

12. STATISTICAL ANALYSIS

12.1 Statistical Methods

All statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute Inc. SAS/STAT, Cary, NC, US) and with WinNonlin® Version 8.3 or higher (Pharsight Corporation, Mountain View, CA, US). Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP, which will be finalised prior to study completion. A general description of the planned methods is provided below. Any deviation from the SAP will be noted and explained in the final study report.

Frequency tables for categorical variables (absolutes and relative frequencies) and descriptive statistics for continuous variables (i.e., number of subjects, mean, SD, minimum, median, quartiles, and maximum) will be calculated. All statistical analyses will be purely descriptive.

12.2 Sample Size and Power Calculations

This study will enrol 30 subjects. The sample size for this Phase 1 study is based on a pragmatic approach. No formal sample size calculation has been conducted.

12.3 Randomisation

This is an open-label study, and no randomisation will be applied. Enrolment is defined as the time of signed informed consent.

12.4 Analysis Sets

12.4.1 Safety Analysis Set

The SAF consists of all enrolled subjects who have received at least 1 dose of investigational product.

12.4.2 PK Set

The PK population is defined as all subjects who have received the investigational product, did not have major protocol deviations or other events that may affect PK, and have sufficient plasma concentration. The PK population will be finalised prior to database lock.

12.5 Background and Demographic Characteristics

The number of subjects enrolled, treated, completed, or discontinued from the study, along with the reason for discontinuation, will be summarised.

In addition, the number of subjects in each analysis set will be tabulated.

Subject demographics and baseline characteristics will be summarised using descriptive statistics on the SAF; no formal statistical analysis tests will be performed.

For quantitative variables the mean, SD, median, minimum and maximum will be calculated. For qualitative variables, frequencies and associated percentages will be tabulated.

Medical history data will be coded using MedDRA and summarised by MedDRA SOC and PT. The data will also be listed, including the verbatim Investigator description of the relevant medical condition, the coded terms (SOC, PT), start date, end date, and whether or not the condition is ongoing.

12.6 Investigational Product

The investigational product will be administered as a single dose of 0.5 μg/kg, 3 times a week over a period of one week. The total amount of investigational product given will be calculated for each subject and will be compared to the amount expected to be given for each subject. Treatment compliance will be calculated for each subject and summarised overall.

In addition, the number and percentage of subjects who were administered 1, 2, or 3 doses will be summarised with the actual dose received at each administration, i.e., on Day 1, 3, and 5.

Results will be summarised on the SAF by means of descriptive statistics (n, mean, SD, median, minimum, quartiles and maximum) for quantitative variables and by means of frequencies and associated percentages for qualitative variables.

12.7 Concomitant Therapy

Medications will be coded using the World Health Organization Drug Dictionary. Counts and percentages of subject use for each concomitant medication will be tabulated by appropriate World Health Organization Drug Dictionary classifications on the SAF. Prior medications will be presented in a listing only using the SAF. Traditional Chinese medicines should also be recorded.

A prior medication is defined as any medication taken any time with an end date before the date of the first administration of investigational product.

A concomitant medication is defined as any medication/therapy used on or after the date of the first administration of investigational product or with a missing end date. If missing, the medication will be assumed to be ongoing and considered as concomitant.

12.8 Pharmacokinetics

All PK analyses will be performed using the PK analysis set.

Noncompartmental PK analysis will be applied to derive all PK parameters in this study.

Plasma difelikefalin concentrations will be summarised descriptively by nominal time at each time point. Individual and mean plasma concentration-time profiles and spaghetti plots (individual subject profiles in one plot) will be provided. In addition, individual plasma difelikefalin concentrations will be listed by subjects.

All PK parameters (e.g., C_{max}, T_{max}, AUC_{0-t}, AUC_{inf}, $AUC_{Extrap(\%)}$, $t_{½}$, clearance, and V_z) will be summarised descriptively. Descriptive statistics will include N, mean (arithmetic and geometric), SD, median, coefficient of variation, minimum, quartiles, and maximum.

12.9 Efficacy Evaluations

Not applicable.

12.10 Safety Evaluations

All safety analyses will be performed on the SAF. Incidence of AEs, AESIs, and SAEs will be tabulated by SOC and PT, using MedDRA coded terms. Incidence of AEs will also be summarised by maximum intensity and maximum relationship to the investigational product. Vital signs, biochemistry, haematology data, and 12-lead ECG recordings will be descriptively summarised by visit as applicable, in addition to change from baseline. Details are listed as below.

12.10.1 Adverse Events

All AEs and pre-treatment AEs will be coded using MedDRA to MedDRA SOC and PT for standardisation and summary purposes.

All reported AEs will be included in summary tables and in by-subject AE listings.

An AE is defined as any AE that has an onset on or after the first investigational product administration, or any pre-existing condition that has worsened on or after the first administration of investigational product.

A pre-treatment AE is defined as any AE that has an onset before the first investigational product administration.

The number and percentage of subjects experiencing AEs, as well as the number of events will be summarised. A subject will be counted only once in the incidence count for a MedDRA SOC or PT, although a subject may have multiple occurrences (start and stop) of an event associated with a specific MedDRA SOC or PT.

In addition, the incidence and percentage of subjects experiencing treatment-emergent SAEs and AEs leading to investigational product discontinuation will be presented by the appropriate MedDRA SOC and PT.

AEs will also be summarised by severity and by relationship to investigational product. If the severity and/or relationship to the investigational product of an AE is missing, a worst-case scenario will be assumed (i.e., the AE will be categorised as “severe” and/or

"related" to the investigational product). If a subject reports the same AE multiple times the event with the worst severity and the strongest relationship to investigational product will be tabulated.

An overall summary table will be provided, presenting the number and percentage of subjects as well as the number of events for AEs, SAEs, treatment-emergent deaths, treatment-related AEs, treatment-related SAEs, severe AEs, AEs leading to investigational product discontinuation and AESIs.

In addition, the following summary tables will be presented and will include the number and percentage of subjects as well as the number of events for:

- AEs by SOC and PT
- SAEs by SOC and PT
- AEs by SOC, PT, and maximum severity
- Related AEs by SOC and PT
- AEs leading to investigational product discontinuation by SOC and PT
- AESIs by PT
- Related AESIs by PT

All AEs will be listed in chronological order, including information such as subject identifier, age, sex, a flag indicating whether the event was treatment-emergent, and all related event status information (start and stop dates, whether the event was ongoing, study day of onset, severity, seriousness, relationship to investigational product, action taken with investigational product, and outcome). Separate listings will be generated for SAEs, deaths, AEs leading to investigational product discontinuation, and pre-treatment AEs. Pre-treatment AEs will not be included in any summary tables.

12.10.2 Special Situations

All special situations will be coded using MedDRA (when applicable).

All reported special situations will be included in a by-subject listing.

12.10.3 Vital Signs

Summary statistics for absolute vital sign value and the changes from baseline will be presented for each visit.

12.10.4 12-lead ECG

Baseline and change from baseline in ECG parameters will be summarised at each post-baseline time point.

All 12-lead ECG data will be listed in a by-subject listing.

12.10.5 Physical Examination

Not applicable as physical examination findings will be recorded through medical history or AEs if clinically relevant.

12.10.6 Clinical Laboratory Tests

Summary statistics for absolute value and the changes from baseline will be presented for each visit and for each laboratory variable. In addition, each reading will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables from baseline to each post-baseline time point measurements will also be presented.

12.11 Other Evaluations

12.11.1 Dialysis Details

Dialysis details will be listed only using the SAF.

12.12 Handling of Missing Data

Procedures for managing missing data, imputation for missing or partially missing data will be provided in the SAP.

Definitions of baseline will be specified in the SAP and will include rules for identification of baseline values when assessments are missing at the scheduled baseline visit.

13. STUDY ETHICAL CONSIDERATIONS

13.1 Ethical Conduct of the Study

The study will be conducted according to the principles of the World Medical Association's Declaration of Helsinki [15], and the ICH guidelines for Good Clinical Practice (GCP) [16] as amended. The Sponsor will ensure that the study complies with all local, federal, or country regulatory requirements.

The Investigator must ensure the anonymity of all subjects participating in the study. Each subject will be assigned a unique subject number, and this should be used on all forms associated with the subject's documents or samples that will be supplied to the Sponsor or any party completing testing on behalf of the Sponsor (e.g., blood for central laboratory assessments).

All anonymous data remains the property of the Sponsor.

13.2 Informed Consent

The ICF used for the study must comply with the Declaration of Helsinki, regulatory and legal requirements of China, and ICH guidelines; and must have been approved by the IEC prior to use. The Investigator or an authorised associate must explain orally and in writing the nature of the study and the treatment in such a manner that the subject is aware of potential benefits and risks. Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects must be provided sufficient time to consider participation, including discussion with family members prior to signing the ICF. Documentation of the discussion and the date of informed consent must be recorded in the source documentation. Subjects must give informed consent in writing. If applicable, consent from female partners (who become pregnant during the study) of male subjects will also be acquired.

13.3 Independent Ethics Committee

The protocol, any protocol amendments and consent form for the proposed clinical study and any other documents required by the local IEC must be submitted by the Investigator for review and approval to the IEC. The Investigator must also ensure that the IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of the approval letter must be forwarded to the Sponsor before the study is implemented.

Approval by the Human Genetics Resources Administration of China will be obtained prior to study initiating for the different study sites.

13.4 Insurance

The Sponsor confirms that it carries liability insurance which protects non-employee physicians or Investigators against claims for which they may become liable as a result of damages caused by Sponsor products used in clinical studies. Insurance coverage is not

extended to damages that the Investigators or third parties may suffer by reason of acts of commission or omission on the part of such Investigators and that are not in accordance with accepted common medical practices (*lege artis* procedures). The Sponsor will reimburse the subject for all study-related injuries provided that the injury does not arise from the subject's misuse of the investigational product or failure to follow the Investigator's instructions.

14. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator must ensure that all trial related site source data, study-related documents and reports will be available, and that the provision of direct access for monitoring and auditing by the Sponsor or its designees will be permitted. In addition, the Investigator must ensure that all trial related site source data, study-related documents and reports will be made available for Sponsor audit and inspection by the appropriate Regulatory Authority and review by the IEC.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the Monitor (source document verification), and the maintenance of a drug dispensing log by the Investigator. The data collected will be entered (double-data entry or EDC) into the study database. A comprehensive validation check program will verify the data and queries will be generated for resolution by the Investigator. Throughout the study, the Sponsor or its designates may review data as deemed necessary.

The following steps will be taken to ensure that the trial is conducted by the investigational site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or
- Investigator site initiation
- Routine site monitoring
- Documented protocol and GCP training
- eCRF and query review against source documents
- Collection of local laboratory normal ranges

14.1 Quality Management: Critical Processes and Data

The following processes and data have been identified during the risk management activities for this trial as critical to ensure human subject protection and the reliability of trial results.

The Sponsor and its designees will ensure a close oversight of the site's activities related to the trial. Throughout the study, the clinical study team will work to ensure that the trial is operationally feasible and focuses on study activities essential to human subject protection and the reliability of trial results, including (but not limited to):

- Study protocol design and implementation
- Tools and procedures supporting data collection and processing

- Tools and procedures safeguarding the rights and protection of human subjects
- Activities essential to trial decision-making and compliance

15. REPORTING AND RECORDING OF DATA

All required study data must be entered in the eCRF created for the study. Training on the system will be provided to all sites, including instructions on how to address missing data, corrections, query procedures, and electronic signatures. Only individuals who are identified on the authorised signature page may enter/correct data in the eCRF. For those subjects who withdraw before completion of the study, all available efficacy and safety data must be entered in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries addressed to the Investigator for resolution.

15.1.1 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which case reports for each subject are based. They are to be separate and distinct from eCRFs. These records should include detailed notes on:

- The medical history
- The basic identifying information, such as demographics, that link the subject's source documents with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The subject's exposure to study treatment
- All AEs and pregnancies
- All special situations as defined in Section 10.8.1
- The subject's exposure to any concomitant therapy (including date and quantity dispensed)
- All relevant observations and data on the condition of the subject throughout the study
- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation

All data for the study must be available in source documentation.

15.1.2 Records Retention

The Investigator must arrange for the retention of all study documentation (such as eCRF files or printed forms, research files, and master files) for the duration specified in their respective site contract or as specified by the applicable Regulatory Authority, whichever is longer. The Sponsor will inform the Investigator in writing when files can be destroyed.

Archived data may be held on DVD, USB, or through a secure file transfer protocol site, or electronic record, provided that a back-up copy exists and that a hard copy can be generated if required.

The Investigator must inform the Sponsor immediately if any documents are lost, to be transferred to a different facility, or to be transferred to a different owner.

15.1.3 Site Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

16. PROCEDURE FOR MODIFICATION OF PROTOCOL OR PREMATURE TERMINATION OF THE STUDY

16.1 Protocol Deviations

The Investigator will not deviate from the protocol without prior written approval from the Sponsor, except in medical emergencies. In the event of a medical emergency, the Investigator must notify the Sponsor Medical Expert as soon as possible. Any other change to the protocol must be implemented as an amendment to the protocol (see Section 16.2). The criteria describing protocol deviation(s) and how they will be handled will be documented in the SAP.

16.2 Protocol Amendments

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of the Sponsor. Each applicable Regulatory Authority/IEC will review and approve amendments prior to their implementation. Regulatory Authority/IEC approval need not be obtained prior to removal of an immediate hazard to subjects.

16.3 Study Termination

The Sponsor reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include (but are not limited to) unsatisfactory subject enrolment with respect to quality and/or quantity, site is unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and/or incomplete.

In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests. Both parties will arrange the procedures on an individual basis after review and consultation and in accordance with the study contract.

17. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The Sponsor is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles [17]. The Clinical Trial Agreement describes the Sponsor's publication terms.

Where possible, authorship will be agreed at the beginning of the study. The authors will form a publication committee and this committee will propose and develop appropriate scientific manuscripts or abstracts from the study data. Investigators may not present or publish partial or complete study results individually. Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by Vifor Fresenius Medical Care Renal Pharma Ltd. before submission for publication. Names of all Investigators participating in the study will be included in the publication.

The publication committee for a study will comprise of authors selected in adherence with the International Committee of Medical Journal Editors criteria for authorship [18]. That is, all authors must meet each of the following 4 criteria:

1. Substantial contribution to the conception and design of the work; or the acquisition, analysis, or interpretation of data for the work; and

2. Drafting the work or revising it critically for important intellectual content; and

3. Final approved of the version to be published; and

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition, certain Sponsor employees involved in the design and conception of the protocol, study management, and data analysis and interpretation are qualified authors and will be included in the publication committee e.g., the lead physician, statistician, and study project manager, or their equivalents.

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