STATISTICAL ANALYSIS PLAN (SAP) - PERIOD: OPEN-LABEL EXTENSION

Investigational Drug:	Difelikefalin (CR845)
Treatment:	Moderate-to-Severe Pruritus in Haemodialysis Subjects
Study Phase:	Phase 3
Study Title:	A Randomised, Double-Blind, Placebo Controlled, Multicentre, Phase 3, Clinical Study of Difelikefalin in Haemodialysis Chinese Adult Subjects with Moderate-to-Severe Pruritus
Protocol Number:	KOR-CHINA-301
Protocol Version:	Version 2.0
Protocol Version date:	29 March 2022
Sponsor:	Vifor Fresenius Medical Care Renal Pharma Ltd. Rechenstrasse 37 St. Gallen CH-9014 Switzerland
SAP Version:	Version 2.0
SAP Version Date:	27 Nov 2024
SAP Author:	PPD

APPROVAL SIGNATURES FOR SAP - PERIOD: OPEN-LABEL EXTENSION

Study Title:	A Randomised, Double-Blind, Placebo Controlled, Multicentre, Phase 3, Clinical Study of Difelikefalin in Haemodialysis Chinese Adult Subjects with Moderate-to-Severe Pruritus
Protocol Number:	KOR-CHINA-301
Protocol Version/Amendment No. and Date (if applicable)**:**	Version 2.0 29 March 2022
New SAP Version and Date	V2.0/27 Nov 2024
Superseded SAP Version and Date (if applicable)**:**	V1.0/12 Aug 2024

As signed below, I approved the Statistical Analysis Plan version 2.0 for the open-label extension of the study: A Randomised, Double-Blind, Placebo Controlled, Multicentre, Phase 3, Clinical Study of Difelikefalin in Haemodialysis Chinese Adult Subjects with Moderate-to-Severe Pruritus.

2024/11/28 | 16:34:13 CST

Prepared by: PPD PPD

SAP Author Signature Date

PPD)

2024/11/28 | 16:48:24 CST

Reviewed by: PPD PPD

Review Statistician Date

PPD

2024/11/28 | 17:13:14 CST

Approved by: PPD PPD

Sponsor Trial Statistician Signature Date

PPD

2024/11/28 | 17:24:45 CST

Approved by: PPD PPD

Sponsor Clinical Research PPD Signature Date

PPD

2024/11/28 | 18:28:34 CST

Approved by: PPD PPD

PPD S Date

PPD

PPD

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

%	Percentage
AE(s)	Adverse event(s)
AESI(s)	Adverse event of special interest(s)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CI	Confidence interval
CKD	Chronic kidney disease
CRF	Case report form
CKD-aP	Chronic kidney disease-associated pruritus
CRO	Contract research organisation
DRM	Data review meeting
ECG	Electrocardiogram
eCRF	Electronic case report form
EoT	End of treatment
ESRD	End stage renal disease
ET	Early Termination
FAS	Full Analysis Set
HD	Haemodialysis
ICF	Informed consent form
IRT	Interactive Response System
IV	Intravenous
LS	Least squares
KOR	Kappa opioid receptor
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
N	Number
NRS	Numerical Rating Scale
OL-SAF	Open-label safety analysis set

PD	Protocol deviation
PRO	Patient reported outcome
PT	Preferred term
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TFL	Tables, figures and listings
WI-NRS	Worst Itching Intensity Numerical Rating Scale

SAP REVISION HISTORY

Version	Effective Date	Summary of Changes
0.1	21Jun2024	Initial version, based on protocol V 2.0, 29-Mar-2022
0.2	24July2024	Updated according to sponsor's comments
0.3	07Aug2024	Updated according to sponsor's comments
1.0	12Aug2024	Version 1.0 finalised
1.1	23Oct2024	Updated according to dry run 1 comments
2.0	27Nov2024	Version 2.0 finalised

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used for the reporting and analyses of the open-label extension period data collected under protocol KOR-CHINA-301 version 2.0 dated 29 March 2022. The statistical analyses for the double-blind period are addressed in a separate SAP.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the SAP has been developed using the protocol dated 29 March 2022 and CRF dated 08 November 2023. Any further changes to the protocol or CRF may necessitate updates to the SAP. Statistical rationale and analysis methods specified in this document take precedence over those described in the protocol, should there be any differences (see Section 1.2 in this document).

1.1 Study Rationale

The number of patients in China undergoing haemodialysis (HD) is increasing. Approximately 42% of HD patients in China are distressed by moderate or severe pruritus. The benefits of the kappa opioid receptor (KOR) agonist difelikefalin in reducing itch in chronic kidney disease-associated pruritus (CKD-aP) patients undergoing HD has been demonstrated in multiple Phase 2 and Phase 3 clinical studies outside of China. Study KOR-CHINA-301 is the first Phase 3 clinical trial of IV difelikefalin for the treatment of subjects with moderate-to-severe CKD-aP on HD to be conducted in China.

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. Treatment with difelikefalin is also expected to relieve pruritus in HD patients in the present study.

This study is designed to evaluate efficacy and safety of 0.5 µg/kg IV difelikefalin in Chinese subjects with CKD on HD (3 times weekly) and with moderate-to-severe associated pruritus. A dialysis frequency of 3 times a week (versus twice weekly), is prevalent for the dialysis practice in China. The single dose of 0.5 µg/kg difelikefalin (administered 3 times weekly), is based on 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. IV administration of difelikefalin occurs at the end of HD by using the return HD line or via injection directly into a vein.

This study consists of a double-blind, randomised, placebo-controlled, parallel group treatment period, and an optional open-label extension period.

During the double-blind period, subjects are to be administered investigational product (difelikefalin or placebo) at the end of each dialysis session for 12 weeks (3 times weekly, 36 times in total). The duration of the double-blind period is enough for the evaluation of the efficacy and safety in comparison with placebo. The primary efficacy endpoint is to be evaluated at Week 4. Twelve-week double-blind treatment is also considered enough for the assessment of difelikefalin safety in comparison with placebo, as adverse reactions occur early during difelikefalin treatment.

At the end of the double-blind period, subjects have the option to enter an open-label extension period, during which difelikefalin is to be administered at the end of each dialysis session for 14 weeks (3 times weekly, 42 times in total). Thus, all subjects completing the double-blind period are to be given the chance to receive the active treatment during the open-label phase if they meet inclusion criteria. The inclusion of 14 weeks open-label treatment increases the total duration of exposure to 26 weeks (for subjects receiving difelikefalin during the double blind and open-label phases) and also increases the safety population, allowing for collection of more safety data. After last administration of investigational product (end of double-blind period or end of open-label extension period or early discontinuation), subjects enter a 1-week follow-up period (1 week to 10 days).

1.2 Changes from Protocol

Regarding the efficacy part, analyses of the number and percentage of subjects that have a 5 point or greater improvement of the 5-D itch scale total score and the number and percentage of subjects that have a 15 point or greater improvement of the Skindex-10 scales total score are added in the SAP.

2 STUDY SUMMARY

2.1 Objectives

2.1.1 Primary Objectives

- To evaluate the efficacy of difelikefalin 0.5 µg/kg compared to placebo in reducing the intensity of itch in HD Chinese subjects with moderate-to-severe pruritus.

2.1.2 Secondary Objectives

- To evaluate the efficacy of difelikefalin 0.5 µg/kg compared to placebo in improving the itch-related quality of life (QoL) in HD Chinese subjects with moderate-to-severe pruritus.
- To evaluate the safety of difelikefalin 0.5 µg/kg in HD Chinese subjects with moderate to-severe pruritus.

2.1.3 Exploratory/Additional Objectives

Not applicable.

2.2 Study Design

This is a Phase 3, multicentre, controlled, randomised study to evaluate the efficacy and safety of difelikefalin 0.5 µg/kg compared to placebo in reducing the intensity of itch in adult Chinese HD subjects with moderate-to-severe pruritus (see Figure 1 - Study Schema below).

The study includes a 12-week double-blind placebo-controlled treatment period and a 14-week optional open-label extension period. A 4-week period (including a 7-day run-in period during the week prior to randomisation) before entry into the double-blind period is defined as the screening period, during which subjects do not receive any investigational product.

During the open-label extension period, difelikefalin is administered for 14 weeks (3 times weekly), starting at Week 13 (or up to 1 week following the double-blind period). The first visit and first dosing for the open-label extension phase of the study occurs immediately on the day of the last visit of the double-blind period or up to 1 week after the end of the double-blind period. The participation in the open-label extension period is optional.

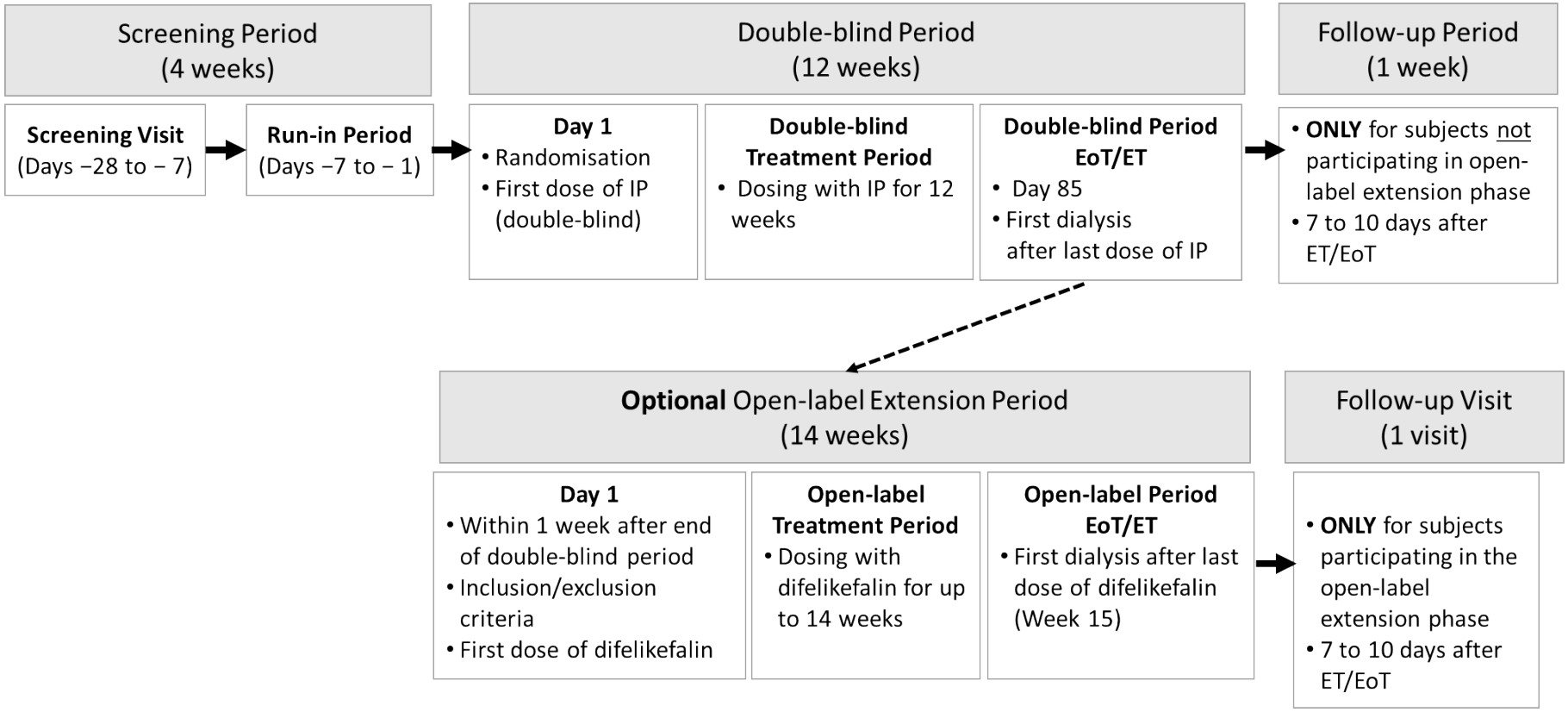
The study also includes a 1-week (1 week to 10 days) follow-up period after last administration of investigational product (end of double-blind period or end of open-label extension period or early discontinuation).

Throughout the study, subjects could continuously use any conditionally permitted concomitant medications (e.g., to treat symptoms of chronic renal failure or other comorbidities) used at the start of the screening period.

Refer to Table 1 - Schedule of Events and Assessments for the Double-blind Period and Table 2 - Schedule of Events and Assessments for the Open-label Extension Period for the frequency and timing of the required study assessments.

2.3 Schedule of Events

Figure 1 Study Schema



Notes: Conditionally permitted concomitant medications (anti-itch drugs) are allowed throughout the study.
EoT=End of treatment; ET=Early termination; IP=Investigational product.

Table 1 Schedule of Events and Assessments for the Double-blind Period

Study Procedures	Screening Period: Screening Visit[1]	Screening Period: Run-in Period[1]	Double-blind Period[2]						Double-blind End Treatment[3]/ Early Termination	Follow-Up Period of (ONLY for Subjects not Participating in Open-label Extension Phase)
Visit Days	Day -28 to Day -7	Day -7 to Day -1	Week 1			Weeks 2 to 12			Week 13	Follow-up Day 1 to 10 after EoT
Study day	-28 to -7	-7 to -1	M/Tu 1	W/Th 3	F/Sa 5	M/Tu	W/Th	F/Sa	85	85 to 95
Administrative Procedures										
Informed consent	X									
Dispense subject identification card	X									
Inclusion/exclusion criteria	X		X[4]							
Medical history/prior medications (including antipruritic medications)/demographics	X	X[4]	X[4]							
Randomisation			X							
Safety and efficacy evaluations										
Physical examination	X									
Prescription dry body weight	X		X							
Pre-dialysis 12-lead ECG[5]	X[5]								X[5]	
Pre-dialysis vital signs	X		X[6]			X[6]			X[6]	X[7]
Haematology, serum chemistry (pre-dialysis)[8]	X		X						X	
Separate serum potassium						X[9]				
Serum pregnancy (females of childbearing potential only)	X[10]								X	
Subject training on PRO worksheets		X[11,12]	X[12]						X	
Worst Itching Intensity NRS (daily)[13]		X	Record on an ongoing basis						X	X[14]
5-D itch scale, Skindex-10 scale[15]			X			X[15]			X[15]	
Patient Global Impression of Change									X	
IV administration of investigational product			Record on an ongoing basis							
Adverse event monitoring	X	X	Record on an ongoing basis						X	X
Concomitant medications (including antipruritic medications)[16]			X	Record on an ongoing basis					X	X

Study Procedures	Screening Period		Double-blind Period[2]						Double-blind End Treatment[3]/ Early Termination	Follow-Up Period of (ONLY for Subjects not Participating in Open-label Extension Phase)
Visit Days	Screening Visit[1] Day -28 to Day -7	Run-in Period[1] Day -7 to Day -1	Week 1			Weeks 2 to 12			Week 13	Follow-up Day 1 to 10 after EoT
Study day	-28 to -7	-7 to -1	1	3	5	M/Tu	W/Th	F/Sa	85	85 to 95
Structured safety evaluation[17]		X		X			X			X

1 Sites have the option to conduct the screening visit during the run-in period at the discretion of the Investigator.
2 Each visit during the double-blind period coincides with the subject's normal dialysis treatments.
3 The end-of-treatment visit in the double-blind phase is the first dialysis visit following the last dose of investigational product (i.e., first dialysis on Week 13 (Day 85)), which also corresponds to Day 1 of the first day of the open-label extension. For subjects not participating in the open-label extension, Day 85 corresponds to Day 1 of the follow-up period.
4 Medical history is to be updated on Day 1 with any changes since the screening visit, and inclusion/exclusion criteria are confirmed prior to randomisation. Antipruritic medication is to be updated at each dialysis visit during the run-in period.
5 12-lead ECG must be performed prior to the start of dialysis at screening, Day 85 (double-blind period end of treatment), or at early termination visit.
6 Pre-dialysis vital signs, including body temperature, heart rate, and blood pressure, are to be recorded on Days 1, 15, 29, 43, 57, 71 and 85 (double-blind period end of treatment), or at early termination visit only when the subject is in a sitting or semi-recumbent position. Heart rate is to be measured at each dialysis; if heart rate is clinically significant at visits outside the pre-specified visits per Schedule of Events, the heart rate is to be recorded in the eCRF.
7 Pre-dialysis vital signs, including body temperature, heart rate, and blood pressure, are to be recorded at the follow-up visit (at 7 to 10 days after EoT/ET visit). Heart rate is to be measured at each dialysis visit during the follow-up period; if heart rate is clinically significant at visits outside the follow-up visit, the heart rate is to be recorded in the eCRF.
8 Blood samples for clinical laboratory evaluation are to be taken at screening, and on Days 1 and 85 (double-blind period end of treatment), or at early termination visit only and are to be assessed at central laboratory. Haematology includes basophil %, basophil (absolute), eosinophil %, eosinophil (absolute), haematocrit, haemoglobin, lymphocyte %, lymphocyte (absolute), MCH, MCHC, MCV, monocyte %, monocyte (absolute), neutrophil %, neutrophil (absolute), platelet, RDW, red blood cells, white blood cells. Serum chemistry will include albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, bilirubin (total), BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, sodium.
9 Serum potassium is to be assessed separately at Weeks 3, 5, 7, 9 and 11 (Days 15, 29, 43, 57 and 71) (central laboratory assessment).
10 Within 7 days prior to first dose of investigational product (central laboratory assessment).
11 Training on Worst Itching Intensity NRS is to be conducted on the first day of the run-in period (Day -7).
12 Training on Skindex-10 scale and 5-D itch scale may be performed at any time during the week prior to randomisation or on Day 1 of the double-blind period.
13 Subjects are requested to complete their Worst Itching Intensity NRS worksheets each day at a similar time (either at home on non-dialysis days around the normal start time of their dialysis or in the dialysis unit). On dialysis days, the worksheets are to be completed prior to or during dialysis, but must be completed prior to dosing.
14 During the follow-up period, Worst Itching Intensity NRS worksheets are to be completed on dialysis days only.
15 5-D itch scale and Skindex-10 scale are to be completed on Day 1 and the first visit of Week 5 (Day 29), Week 9 (Day 57) and Week 13 (Day 85). 5-D itch scale will preferably be completed first. If the first visit of the week is missed, the subject may complete the worksheets at their next visit for the same week. The worksheets are to be completed prior to or during dialysis (preferably within 1 hour of the dialysis) but must be completed prior to dosing.
16 Concomitant medications including antipruritic medication are to be updated at each dialysis visit during the double-blind period, and until the end of the follow-up period.
17 A list of specific signs/symptoms is to be verified with the subject by qualified site staff, preferably to be completed on Wednesday/Thursday each week during the run-in period, the double-blind period, and the discontinuation period. Not to be completed on Monday/Tuesday (see Protocol Section 10.8.4.1 for a list of the AESIs).

Notes: AESI=Adverse event of special interest; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; BUN=Blood urea nitrogen; ECG=Electrocardiogram; eCRF=Electronic Case Report Form; EoT=End of treatment; F=Friday; IV=Intravenous; M=Monday; MCH=Mean corpuscular haemoglobin; MCHC=Mean corpuscular haemoglobin concentration; MCV=Mean corpuscular volume; NRS=Numerical Rating Scale; PRO=Patient reported outcome; RDW=Red blood cell distribution width; S=Saturday; SGOT=Serum glutamic-oxaloacetic transaminase; SGPT=Serum glutamic-pyruvic transaminase; Th=Thursday; Tu=Tuesday; W=Wednesday.

Table 2 Schedule of Events and Assessments for the Open-label Extension Period

Study Procedures	Open-label Treatment Period[1]							EoT/ Early Termination	Follow-Up
	Day 1[2]	Week 2[1]	Week 4[1]	Week 6[1]	Week 8[1]	Week 10[1]	Week 12[1]	First Dialysis of Week 15[3]	7 to 10 Days After EoT/ Early Termination[4]
Inclusion/exclusion criteria	X[5]								
Physical examination	X								
Prescription dry body weight[6]	X						X		
Pre-dialysis 12-lead electrocardiogram[7]								X	
Pre-dialysis vital signs[8]	X		X		X		X	X	X
Haematology, serum chemistry (pre-dialysis)								X	
Serum potassium (pre-dialysis)		X	X	X	X	X	X		
Serum pregnancy test for women of childbearing potential only								X	
5-D itch scale, Skindex-10 scale[9]			X		X		X	X	
IV administration of investigational product	After each dialysis, up to Week 14 included								
Adverse event monitoring	Record on an ongoing basis[10]								
Concomitant medications (including antipruritic medications)	Record on an ongoing basis[10]								

1 Each visit during the open-label treatment period coincides with the subject's normal dialysis treatments. The study visit may occur on any chosen dialysis day of a scheduled week if all assessments are completed during that visit.
2 Day 1 of the open-label treatment period corresponds to the day of the last visit of the double-blind period or up to 1 week following the double-blind period.
3 The end-of-treatment visit is the first dialysis visit following the last dose of investigational product (i.e., first dialysis on Week 15).
4 The follow-up visit coincides with a dialysis day.
5 Prior to dosing on Day 1 of the open-label treatment period, the inclusion/exclusion criteria are confirmed.
6 The prescription dry body weight is captured from the dialysis prescription and recorded on Day 1 and at Week 12. If there is a >10% change in prescription dry body weight compared to the last value, then the difelikefalin dose will be adjusted.
7 Electrocardiogram must be performed prior to the start of dialysis.
8 Vital signs, including body temperature, heart rate, and blood pressure, are obtained at the specified visits while the subject is in a sitting or semi-recumbent position prior to the start of dialysis. Heart rate is measured at each dialysis; if the heart rate is clinically significant at visits outside the pre-specified visits per Schedule of Events, the heart rate is to be recorded in the eCRF.
9 To be completed before or during dialysis (preferably within 1 hour of the dialysis but before dosing). 5-D itch scale is preferably to be completed first.
10 Adverse events and concomitant medications are recorded starting on Day 1 of the open-label treatment period.

Notes: eCRF=Electronic Case Report Form; EoT=End of treatment; IV=Intravenous.

2.4 Sample Size Determination

Double-blind Period

In a Japanese Phase 2 clinical study (MR13A9-4), a mean difference of -1.0 was observed between the difelikefalin and placebo groups, with an SD of 2.09 and 1.98 in the difelikefalin and placebo groups, respectively, regarding the change from baseline in the weekly mean of the daily 24-hour worst itching intensity numerical rating scale (WI-NRS) score at end of Week 4.

In the pooled data of 2 Phase 3 clinical studies (CLIN3102 and CLIN3103), a mean difference of -0.8 was observed between difelikefalin and placebo groups with an SD of 2.15 and 1.99 in the difelikefalin and placebo groups, respectively, regarding the change from baseline in the weekly mean of the daily 24-hour WI-NRS score at end of Week 4.

Based on the results observed at the end of Week 4 in previous studies as mentioned in the above paragraphs, a mean difference of -0.9 with a common SD of 2.1 is assumed between difelikefalin and placebo groups regarding the primary endpoint. Assuming a 2-sided significance level of 5% and a statistical power of 90%, 116 subjects per group are required to detect a difference of -0.9, with a common SD of 2.1, between the difelikefalin and the placebo groups using a 2-sample t-test. In addition, assuming, a 10% drop out rate, 258 subjects in total need to be enrolled in the double-blind study period, i.e., 129 subjects per group.

Open-label Extension Period

All subjects who have completed the double-blind period may continue into the 14-week open label extension period if they meet the eligibility criteria at Day 1 of the open-label extension period. Subjects not meeting these inclusion criteria will be withdrawn from the study and undergo the follow-up assessments.

2.5 Randomisation and Blinding

Randomisation and blinding are not applicable for the open-label extension period.

2.5.1 Interim Analysis

No interim analysis will be performed.

The final analysis of the double-blind period is to be performed when all subjects completed or discontinued the double-blind period.

The final analysis of the open-label extension period is to be performed when all subjects completed or discontinued the study.

2.6 Study Endpoints

2.6.1 Efficacy Endpoint for Double-blind Period

The primary efficacy endpoint and secondary efficacy endpoints during the double-blind period are addressed in the double-blind period SAP.

2.6.2 Efficacy Endpoint for Open-label Extension Period

- Change from baseline in itch-related QoL at each time point of the open-label extension phase, as assessed by the 5-D itch scale total score.
- Change from baseline in itch-related QoL at each time point of the open-label extension phase, as assessed by the Skindex-10 scale total score.

2.6.3 Exploratory Efficacy Endpoint

Not applicable.

2.6.4 Safety Endpoints

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.

3 ANALYSIS SETS

The open-label safety analysis set (OL-SAF) consists of all subjects who receive at least 1 dose of investigational product in the open-label extension period. Subjects in the OL-SAF are to be analysed according to the actual treatment sequence received during the double-blind and open-label extension periods (i.e. Placebo/Difelikefalin, Difelikefalin/Difelikefalin) and all sequences pooled (i.e. in total for all patients in the OL-SAF). The OL-SAF is to be used to analyse exposure data to difelikefalin, efficacy and all safety endpoints collected during the open-label extension period.

The full analysis set (FAS) is defined as all subjects who satisfy the following criteria:

- Randomised to treatment
- Received at least 1 dose of investigational product
- Had a non-missing baseline assessment for the weekly mean of the daily 24-hour WI-NRS score

The FAS is to be used to analyse protocol deviations during the study. Subjects in the FAS are to be analysed according to the planned treatment sequence received during the double-blind and open-label extension periods (i.e. Placebo/Difelikefalin, Difelikefalin/Difelikefalin) and all sequences pooled (i.e. in total for all patients). Subjects asssigned to Placebo or Difelikefalin in the double-blind period that did not enter the open-label extension period are counted under Placebo/Difelikefalin or Difelikefalin/Difelikefalin, respectively.

4 DESCRIPTION OF THE STATISTICAL ANALYSIS

4.1 General Considerations

The software used for all summary statistics and statistical analyses is SAS® Version 9.4 or later (SAS Institute, Inc. SAS/STAT, Cary, NC, US).

Medical history, AEs, and special situations (if applicable) are to be coded using the MedDRA version 26.0. Prior and concomitant medications are to be coded using the World Health Organization (WHO) Drug Dictionary version Global B3 March 2023. Versions of dictionaries are to be indicated in the footnote of the relevant tables and listings.

For the purpose of conversion of year/month to days, the following convention will be used:

- 1 year = 365.25 days
- 1 month = 30.4375 days

4.1.1 Standard Descriptive Statistics

Continuous Variables

Unless specified otherwise, the following standard descriptive statistics will be provided for continuous variables by treatment sequence: number of subjects with a non-missing value of the variable (n), number of subjects with a missing value of the variable, mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, and maximum.

Categorical Variables

Unless specified otherwise, the following standard descriptive statistics will be presented for categorical values by treatment sequence: number of subjects with non-missing data, number of subjects with missing data as well as the number and percentage within each category of the parameter. The 'missing' category will not be included in the percentage computation, unless otherwise specified. Details will be defined in the table shells. If no subjects fall in any categories, "0" will be reported.

By convention, for a variable the sum of the number of subjects with non-missing and missing data will always be equal to the number of subjects specified in the header of the corresponding summary table, unless otherwise specified.

4.1.2 Definition of Baseline, Visits and Visit Windows

In general, the baseline is defined as the last available (non-missing) value (scheduled or unscheduled) prior to the first dose in the open-label extension period. For the efficacy endpoints, the 5-D itch scale and the Skindex-10 scale score, analyses will be conducted based on two different baseline definitions. The first definition is that baseline is the last available (non-missing) value (scheduled or unscheduled) prior to the first dose in the open-label extension period. The second definition is that baseline is the last available value (scheduled or unscheduled) before or on the same day as randomisation or if missing as any values during Week 1 (<=Day 7).As a general rule for safety and efficacy related summaries (e.g., tables), the visit label mentioned in Table 3 will be used to present the corresponding data by study visits for the open-label extension period.

Table 3: Study Visits and Planned Assessment Window for Safety and Efficacy Analysis

Visit	Visit Label	Planned Target Day (Assessment Time Window) for by visit parameters
EoT (Double-blind) / Day 1 (Open-label)	Baseline (Open-label)	Day 1 (≤ Day 1) [a]
Week 2 (Open-label)	Open-label Week 2	Day 8 to Day 14 (Day 8 to Day 21)
Week 4 (Open-label)	Open-label Week 4	Day 22 to Day 28 (Day 22 to Day 35)
Week 6 (Open-label)	Open-label Week 6	Day 36 to Day 42 (Day 36 to Day 49)
Week 8 (Open-label)	Open-label Week 8	Day 50 to Day 56 (Day 50 to Day 63)
Week 10 (Open-label)	Open-label Week 10	Day 64 to Day 70 (Day 64 to Day 77)
Week 12 (Open-label)	Open-label Week 12	Day 78 to Day 84 (Day 78 to Day 91)
EoT/ET (Open-label)	Open-label Week 14	Day 99 (Day 92 to maximum day of [Day EoT/ET visit and Day 99])
	Last Post-baseline (Open-label) [b]	
Follow-up (Open-label)	Follow-up (Open-label) [c]	EoT/ET visit + 7 Days ([EoT/ET visit + 1] to maximum day of [EoT/ET visit + 10, 109])

[a] Study Day 1 is defined as the first dose date during the open-label extension period (as per the "Study Drug Administration- Open Label" eCRF page).

[b] The last post-baseline visit is defined as the latest value recorded for a given parameter, not including the Follow-up Visit or any visits following the End of Treatment/Early Termination Visit. To be displayed for safety endpoints summary tables.

[c] Follow-up (Open-label) is applicable for safety analysis only.

4.1.3 Planned Assessment Windows

Assessments collected by study week that are collected at early termination visit and unscheduled visits will be assigned to a planned visit window. If the early termination or unscheduled visit day falls into an assessment time window, it will be mapped to the corresponding scheduled analysis visit. Should more than one measurement fall within a visit window, priority is given first to the measurement with a non-missing value in the following order: first, the scheduled assessment; second, an early termination visit; and next, the unscheduled assessment closest to the planned day. In the case that two unscheduled visits are equidistant, the latest will be used. This rule will be applied both to efficacy and safety endpoints. For detailed assessment time window information, please see the above Table 3.

4.1.4 Treatment Start/Stop Dates

Treatment start date will be taken from the "Study Drug Administration-Open Label" eCRF page.

Treatment stop date will be taken from the "Treatment Termination" eCRF page.

Treatment start and stop dates will not be imputed.

4.1.5 Tables and Listings Presentation

Analyses will be performed according to the actual treatment sequence received during the double-blind treatment and open-label extension periods. Treatment sequences 'Placebo/Difelikefalin' and 'Difelikefalin/Difelikefalin' and all sequences pooled will be displayed in the summary tables and figures. The order of the treatment sequence will be as shown below.

1. Placebo/Difelikefalin
2. Difelikefalin/Difelikefalin
3. Total

The listings will display all the open-label extension period data contained in the eCRF, as well as derived variables.

For continuous variables, rounding in the tables, figures and listings (TFLs) will be defined for each parameter or variable (please refer to Appendix 2) and the following general rules will be applied:

- The minimum and maximum will be reported with the same number of decimal places as the number of decimals mentioned in Appendix 2.
- The Q1, Q3, mean and median will be reported with 1 more decimal place than the number of decimals mentioned in Appendix 2.
- The SD will be reported with 2 more decimal places than the number of decimals mentioned in Appendix 2.

For categorical variables descriptive statistics, percentages will be presented to 1 decimal place. Percentages will not be presented for zero counts, 100 will be presented with no decimal.

4.1.6 Analysis Populations

Please refer to Section 3 for analysis set.

4.1.7 Pooling of Sites/Country

- Not applicable, this study involves only China as country.

4.1.8 Analysis of Subgroups

- Not applicable.

4.1.9 Methods for Handling and Imputation of Missing Data

Missing data for adverse events (AEs) start and end dates, relationship to study drug, severity, and seriousness, disease diagnosis date or starting dates and laboratory values reported as below the limit of detection or below the limit of quantification or above the upper limit of quantification or above the limit of detection, will be handled as described in this section. No other data will be imputed.

For computation of the time since disease diagnosis (CKD or ESRD) or time on hemodialysis or duration of CKD-associated pruritus, missing dates for disease diagnosis or starting dates will be imputed as follows:

- Completely missing date: no imputation.
- If the month of the date is missing, the month will be imputed to January.
- If the day of the date is missing, the day will be imputed to 1st.
- If the imputed date of first haemodialysis is prior to the imputed or actual CKD date, then set the imputed date of first haemodialysis to the CDK date.

Missing and/or incomplete dates/times for events from “Adverse Event” eCRF page are imputed in a manner resulting in considering them as AEs, which is the worst-case scenario. Stop dates/times will not be imputed if the AE is ongoing.

For identification of AEs, partial, or missing dates for AEs will be imputed as follows:

- Incomplete start date: if the day and month are missing and the year is the same as first administration of study drug of double-blind period, or if only the day is missing, and month and year are the same as first drug administration of double-blind period then the start date is to be replaced by the minimum between first drug administration date of double-blind period and AE resolution date. In all other cases the missing start day or start month is replaced by 01.
- Completely missing start date: the start date is replaced by the minimum between first drug administration date of double-blind period and AE resolution date.
- Incomplete stop dates (month and year available or only year available): these dates are imputed to the last day of the corresponding month, or the last day of the corresponding year if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used to impute the incomplete stop date. In all other cases the incomplete stop date is not imputed.

No other dates will be imputed.

For AE summary tables, a worst-case approach will be followed in the event of missing severity, seriousness, or causality data. If the severity is missing, ‘Severe’ will be imputed. If the seriousness is missing, “Serious”

will be imputed. If causality data is missing, 'Related to study medication' will be imputed, exception to this rule will be made for AEs of negative COVID-19 test which will be assumed not to be related to study medication. In the event that no coding information is available for a specific AE, the AE will be presented as an 'Not Coded' in summary tables.

In the laboratory analysis dataset and for the computation of the laboratory summary statistics, the values reported as below the limit of detection or below the lower limit of quantification or above the upper limit of quantification or above the limit of detection will be imputed for all visits, excepted for baseline. Laboratory values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded.

For all calculations,

- laboratory values expressed as 'less than' or 'greater than' will be imputed using the next numerical value (e.g., '<2.00' will be imputed as 1.99, '>0.3' will be imputed as 0.4).
- laboratory values expressed as 'less or equal than' or 'greater or equal than' will be imputed using the numerical value (e.g., '≤2.00' will be imputed as 2, '≥0.3' will be imputed as 0.3).

4.2 Subject Disposition

Subject disposition data will be collected on the "Treatment Termination" and "Study Termination" eCRF pages when a subject completed or discontinued from the treatment and study respectively.

The number of subjects entered the open-label extension period, treated, not treated, completed treatment, or early discontinued treatment from the open-label extension period and from the study during the open-label extension period, along with the discontinuation reasons are to be summarised by treatment sequence and all sequences pooled for the open-label extension period. Additionally, subjects who completed the study will be reported. The following provides the definitions of the aforementioned groups:

- Subjects who entered the open-label extension period are all subjects with a "Yes" noted for the question "Will the subject enter the open-label extension?".
- Treated subjects are all subjects who received at least one dose of open-label study drug.
- Subjects who completed treatment are all treated subjects with a "No" noted for the question "Did the subject discontinue the treatment prematurely?".
- Subjects who discontinued treatment are all treated subjects with a "Yes" noted for the question "Did the subject discontinue the treatment prematurely?".
- Subjects who completed the study are all treated subjects with a "Yes" noted for the question "Did the subject complete the study as per protocol?".
- Subjects who discontinued the study are all treated subjects with a "No" noted for the question "Did the subject complete the study as per protocol?".

For all categories, percentages will be calculated using the number of OL-SAF as the denominator.

The number and percentage of subjects having at least one important protocol deviation (PD) during all study periods will be summarized within each category and subcategory of deviations using FAS.

The number and percentage of subjects having at least one not-important PD during all study periods will be summarized within each category and subcategory of deviations using FAS.

The following data will also be presented in the listings:

- Subject disposition data to be presented in a by-subject listing for OL-SAF.
- Inclusion criteria not met/exclusion criteria met data at Day 1 of the open-label extension period to be presented in a by-subject listing for all subjects entered open-label extension period. The subjects are those who with a "Yes" noted for the question "Will the subject enter the open-label extension?" on the "Confirmation to enter open label" eCRF page.
- All the protocol non-compliance data during the open-label extension period will be listed in a by-subject listing for full analysis set.

4.3 Demographics and Baseline Subject Characteristics

Demographic and baseline characteristics were not re-assessed at the start of the open-label extension period, but will be reported for the OL-SAF summarizing data collected prior to the first dose of double-blind period.

Prescription dry body weight is the exception and will be reported both for the double-blind and open-label extension baselines.

Demographic and baseline disease characteristics are to be summarised descriptively by treatment sequence and all sequences pooled for OL-SAF population.

Demographics and baseline characteristics to be summarised include: age (years) at informed consent as a continuous and categorical variable (≥18 - <65, ≥65 - <85, ≥85 years); gender; race; "If Chinese, both parents are Chinese?" (Yes, No); prescription dry body weight (kg) at double-blind period baseline; prescription dry body weight (kg) at open-label extension period baseline.

All demographic and baseline characteristics data will be provided in by-subject listings.

Baseline disease characteristics variables to be summarised include: baseline weekly mean of the daily 24-hour WI-NRS score, baseline weekly mean of the daily 24-hour WI-NRS score category (moderate (WI-NRS ≥4 to <7) vs. severe (WI-NRS ≥7), use/non-use of anti-itch medication during the week prior to randomisation (randomisation stratum), presence/absence of specific medical conditions (randomisation stratum), aetiology of CKD, dialysis type (all reported types and hemodialysis only vs. any other type, dialysis types recorded as other will be reviewed by medical and programmatically categorised as: HD, HDF, HD/HDF, HD/HP, HD/HDF/HP. HDF is the abbreviation for Hemodiafiltration, and HP is the abbreviation for Hemoperfusion), time since first diagnosis of CKD (years), years on hemodialysis, time since the diagnosis of end stage renal disease (ESRD) (years), duration of CKD-associated pruritus (years).

Time (years) since diagnosis date or duration of CKD- associated pruritus as well as time on hemodialysis will be derived as:

$$\frac{date\ of\ randomisation - date\ of\ diagnosis\ or\ start\ date\ of\ CKD\ \text{associated pruritus or hemodialysis} + 1}{365.25}$$

For handling of missing or partial dates regarding the diagnosis date or the start date, please refer to Section 4.1.9.

All baseline disease characteristics data will be provided in by-subject listings.

4.4 Medical History and Concurrent Medical Conditions

Medical history was not re-assessed at the start of the open-label extension period, but will be reported for the OL-SAF population.

Medical history and concurrent medical conditions are to be summarized for the OL-SAF population.

Medical history will be collected on the "Medical History" eCRF page. Medical history will be coded using MedDRA and summarised by MedDRA System Organ Class (SOC) and Preferred Term (PT), and by treatment sequence and all sequences pooled. Text "Not Coded" will be displayed in case terms are not coded.

The data will also be listed for OL-SAF population, including the verbatim Investigator description of the relevant medical condition, the coded terms (SOC, PT), start date, end date, whether or not the condition is ongoing and treated.

4.5 Prior and Concomitant Medications and Procedures

4.5.1 Prior and Concomitant Medications

Prior and concomitant medications are to be summarized for OL-SAF population.

Prior and concomitant medications will be collected on the "Prior and Concomitant Medications" eCRF page. All medications will be coded using the World Health Organization Drug Dictionary.

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 in the double-blind period. Note that these are identical to the prior medications for the double-blind analyses, but subset to the OL-SAF population.

A concomitant medication during the open-label extension period is defined as any medication/therapy taken from the first dose administration of investigational product in the open-label extension period through the end of treatment or early termination visit of the open-label extension period.

Counts and percentages of subjects use for each concomitant medication during open-label extension period will be tabulated by ATC Level 2 and ATC Level 4 and by treatment group.

In addition, prior and concomitant antipruritic medications during the open-label extension period will be summarized separately by ingredient and by treatment sequence and all sequences pooled. These medications will be selected using “reason for treatment” = "Disease under study" collected on the “Prior and Concomitant Procedures” eCRF page; however, a medical review will be performed to ensure correctness.

Any prior medication and any concomitant medication collected on the eCRF will be presented in a by-subject listing.

4.5.2 Prior and Concomitant Procedures

Prior and concomitant procedures will be collected on the “Prior and Concomitant Procedures” eCRF page. All the prior and concomitant procedures collected on the eCRF will be presented in a by-subject listing.

4.6 Study Drug Exposure and Compliance

Study drug exposure and compliance are to be summarized and listed for OL-SAF population.

Study drug exposure data during open-label extension period will be collected on the “Study Drug Administration-Open label” eCRF page and the dialysis data will be collected on the “Dialysis-Open label” and “Dialysis Type Adjustment” eCRF page. Note that dialyses after last dose may be collected on the “Dialysis-Open Label” eCRF page. Only dialysis from open-label extension period Day 1 until the last dialysis prior to EoT or ET visit will be included as dialysis during the open-label extension period.

For this study, the duration of open-label treatment for each individual subject is expected to be 14 weeks, for a total of approximately 42 doses of study drug administered immediately following each dialysis session. The last day of the open-label treatment period will be defined as the day of the last injection of investigational product + 2.5 days, as there would be 2-3 days from the last dose to the next dialysis.

Study drug administration and treatment compliance during the open-label extension period is to be summarised by treatment sequence and all sequences pooled by the following parameters:

- Duration of open-label treatment (days): calculated as (date of the last dose + 2.5) – (date of first dose) + 1
- Total number of doses actually received as continuous and categorical variables (1-3, 4-6, 7-9, etc.)
- Number of missed doses as continuous and categorical variables (1-3, 4-6, 7-9, etc.)
- Average dose per administration (mcg/kg): calculated as actual dose (ml) * 50 mcg/ml (strength) / prescription dry body weight (kg). Noted the prescription dry body weight is to be captured on Day1 and at Week 12 during the open-label extension period. The most recent value is to be used for the calculation.
- Average dose per administration (mcg): calculated as actual dose (ml) * 50 mcg/ml (strength)
- Number of subjects with extra doses: (1, 2, 3, >=4 doses)
- Compliance (%): calculated as actual doses/planned doses (defined below)

Dialysis performed during the open-label extension period is to be summarized by treatment sequence and all sequences pooled by the following parameters:

- Total number of dialysis visits logged as a continuous and categorical variable (1-3, 4-6, 7-9, etc.)
- Number of missed dialysis visits as a continuous and categorical variable (1-3, 4-6, 7-9, etc.)
- Number of subjects with extra dialysis: (1, 2, 3, >= 4 doses)

- Dialysis Compliance (%): calculated as sum of the actual dialysis visits/sum of the planned dialysis visits (defined below)

Per protocol, if a subject receives additional dialysis during a given week for any reason, an additional dose of investigational product will be administered following dialysis. A maximum of 4 doses per week is allowed. No additional doses will be given for subjects receiving an additional unscheduled ultrafiltration treatment.

The number of planned doses/dialyses will be derived as follows:

- Step 1: For subjects who completed treatment with a "No" noted for the question "Did the subject discontinue the treatment prematurely?", number 42 (14 weeks and 3 times for each week) is assigned. For subjects who did not complete the open-label extension period, the following steps will be applied.
- Step 2: Keep all the doses/dialyses data during open-label extension period for each subject.
- Step 3: Check how far they were into the time point of the last dose/dialysis during the open-label extension period. For example, if the time point is "Week 8-Scheduled First", then the planned dose/dialysis is calculated as 22 times (7 weeks * 3 times/week + 1 time in week 8). If the time point is "Week 9-Scheduled Third", then the planned dose/dialysis is calculated as 27 times (8 weeks * 3 times/week + 3 times in week 9).

Missed doses/dialyses will be determined as follows:

- Step 1: Keep all the doses/dialyses data during open-label extension period for each subject.
- Step 2: Determine the last time point during the open-label extension period for each subject.
- Step 3: Create a dummy dataset with each time point for each subject. For subject who completed treatment with a "No" noted for the question "Did the subject discontinue the treatment prematurely?", number 42 (14 weeks and 3 times for each week) is assigned. For subjects who did not complete the open-label extension period, the following steps will be applied.
- Step 4: Merge the dummy dataset with the dataset including subjects' actual doses/dialyses by each subject and each time point.
- Step 5: Count the number of time points with no actual doses/dialyses for each subject.

Extra doses/dialyses will be determined as follows:

- Step 1: Keep all the doses/dialyses data during open-label extension period for each subject.
- Step 2: Extra doses/dialyses are collected as records with time point = "Unscheduled Visit".
- Step 3: In case of the unexpected circumstance that are multiple records for a specific scheduled time point, only one time would be considered as the planned dose/dialysis, the other doses/dialyses would be considered as "extra".
- Step 4: Sum the "extra" times from step 2 and step 3.

All the dialysis data and dialysis type adjustment after the first dose date in the open-label extension as well as dialysis type adjustment data will be presented in listings.

All the study drug administration, study drug exposure, dialysis, and compliance data of the open-label extension period will be presented in listings.

4.7 Efficacy Analyses

Itch-related QoL including 5-D itch scale and Skindex-10 scale will be collected for the evaluation of the efficacy in the open-label extension period.

4.7.1 5-D Itch Scale

The 5-D Itch Scale was developed as a brief, multidimensional questionnaire designed to be useful as an outcome measure in clinical trials. The 5 dimensions of itch being assessed are degree, duration, direction, disability, and distribution (see protocol Appendix 4).

The duration, degree, and direction domains each include 1 item, while the disability domain has 4 items. All items of the first 4 domains were measured on a 5-point Likert scale. The distribution domain included 16 potential locations of itch, including 15 body part items and 1 point of contact with clothing or bandages.

Single-item domain scores (duration, degree, and direction) are equal to the value indicated below the response choice (range 1-5). The disability domain includes 4 items that assess the impact of itching on daily activities: sleep, leisure/social activities, housework/errands, and work/school. The score for the disability domain is calculated by taking the highest score on any of the 4 items. For the distribution domain, the number of affected body parts is tallied (potential sum 0-16), and the sum is sorted into 5 scoring bins: sum of 0-2 = score of 1, sum of 3-5 = score of 2, sum of 6-10 = score of 3, sum of 11-13 = score of 4, and sum of 14-16 = score of 5.
The scores of each of the 5 domains are calculated separately and then summed together to obtain a total 5-D score. 5-D scores can potentially range between 5 (no pruritus) and 25 (most severe pruritus).
Total 5-D Itch score = duration score (single item) + degree score (single item) + duration score (single item) + maximum (4 disability items) + category score based on sum of affected body parts.
The scoring manual does not give specific direction regarding scoring when some questions are missing; therefore, each domain and the total score will be set to missing when any of their individual components are missing, with the exception of the disability domain. The maximum of any items present for disability will be used for that domain.
Analyses

The 5-D itch scale scores will be analysed using an MMRM model. The model will contain treatment sequence, week, and treatment-by-week interaction as fixed effects, and baseline score and the randomization stratification variables as covariates.

Two independent analyses will be presented, one using baseline from the open-label extension period and one using baseline from the double-blind period. The first analysis will include all visits in the open-label extension period, with the first baseline definition defined in section 4.1.2. The second analysis will include all visits from both the double-blind and open-label periods, with the second baseline definition defined in section 4.1.2.

Separate models will be used for the 2 different changes from baselines described above. An unstructured covariance matrix will be used to model the within-subject errors. Should the model fail to converge, a compound symmetric covariance matrix will be used instead. The Kenward-Roger2 approximation will be used to estimate the denominator degrees of freedom. Missing scores will not be imputed. Assuming that the data are missing at random (MAR), the estimates calculated from the MMRM described above are unbiased.

Standard descriptive statistics will be reported for each time point on the values and changes from baseline along with the least squares (LS) means, standard errors, 95% confidence intervals (CIs), and differences from baseline within each treatment sequence reported with LS means, standard errors, and 95% CIs. Plots will also be created.

The above analyses for the 5-D itch scale total score will be repeated for each of its domain scores.

As a separate analysis, the number and percentage of subjects that have a 5 point or greater improvement of the 5-D itch scale total score will be reported by visit and treatment sequence. Additionally, the percentage and 95% CIs estimated using a logistic regression model, containing terms for treatment sequence, baseline total 5-D score, use of anti-itch medication during the week prior to randomization, and presence of specific medical conditions, will be presented. This analysis will be performed using the baseline from the double-blind period.

4.7.2 Skindex-10 scale

Skindex-10 Scale
Developed specifically for uremic pruritus, the Skindex-10 Scale (see protocol Appendix 3) is an instrument for measurement of quality of life. Subjects are asked the question “During the past week, how often have you been bothered by” and respond by filling in 1 of 7 circles numbered from 0 (labelled with the anchor phrase “never bothered”) to 6 (labelled as “always bothered”) for each of the 10 questions.
The total score is the sum of the numeric value of each answered question.
Additionally, the total score is subdivided into 3 domain scores, which are sums of the scores of the following questions: disease domain (questions 1 to 3), mood/emotional distress domain (questions 4 to 6), and social functioning domain (questions 7 to 10).
The scoring manual does not give specific direction regarding scoring when some questions are missing; therefore, the three domains and the total score will be set to missing when any of their individual components are missing.

Analyses
The analyses for the Skindex-10 scales total score as well as the domain scores will be the same as the 5-D itch scale. The same MMRM model will be used in two independent analyses using different time points for the baseline values and changes from baseline using each of the baselines, as described for 5-D itch in Section 4.7.1. As a separate analysis, the number and percentage of subjects that have a 15 point or greater improvement of the Skindex-10 scales total score will be reported by visit and treatment sequence. Additionally, the percentage and 95% CIs estimated using a logistic regression model, containing terms for treatment sequence, baseline Skindex-10 scales total score, use of anti-itch medication during the week prior to randomization, and presence of specific medical conditions, will be presented. This analysis will be performed using the baseline from the double-blind period.

4.8 Safety Analyses

All safety analyses are to be performed by treatment sequence and all sequences pooled using the OL-SAF and are to be descriptive. Missing values will not be imputed unless stated otherwise, please refer to Section 4.1.9.

4.8.1 Adverse Events

AEs data are collected from the time the informed consent form (ICF) is signed by the subject. The AE reporting period ends at the last study contact. Missing dates/partial dates of AEs will be handled as per Section 4.1.9.

AEs relative to the open-label extension period are identified as any AE with an onset date on or after the first dose of difelikefalin in the open-label extension period.

All tabular adverse event summaries will only include AEs relative to the open-label extension period.

An AE will be classified as related to study drug if the relationship to study drug was recorded as 'Certain' or 'Probable/Likely' or 'Possible' in eCRF, as determined by the investigator. An AE will be classified as unrelated to study drug if the relationship to study drug was recorded as ‘Unlikely’ or ‘Unrelated’ in eCRF as determined by the investigator.

An SAE is defined as an AE when “Is this AE considered as Serious?” on the “Adverse Event” eCRF page is “Yes”.

An AE leading to investigational product interruption is defined as an AE where the action taken with study drug is “Drug Interrupted” on the “Adverse Event” eCRF page. An AE leading to investigational product discontinuation is defined as is defined as an AE where the action taken with study drug is “Drug Withdrawn” on the “Adverse Event” eCRF page. An AE leading to early study termination is defined as an AE where other action taken is “Early Study Termination”.

Adverse Events of Special Interest (AESI)

An AESI is a medical occurrence specific to the product or program. Any AE with the following MedDRA PT is to be identified as an AESI:

- gait disturbance
- fall
- dizziness
- somnolence
- seizure
- syncope
- mental status changes
- mood altered
- feeling abnormal
- sinus tachycardia, tachycardia, and tachyarrhythmia
- palpitations

The number and percentage of subjects experiencing AEs will be summarised by treatment sequence and all sequences pooled. AEs will be summarised by severity. In the instance where a subject reports the same AE multiple times then the event with the worst severity will be tabulated. AEs will also be summarised by relationship to investigational product. In the instance where a subject reports the same AE multiple times then the event with the strongest relationship to investigational product will be tabulated. AEs will be reported on a per-subject and per-event basis. On a per-subject basis this means a subject contributes only once to the count for a given AE (MedDRA SOC or PT using the worst severity and the strongest relationship). The number of events will be reported as well in the summary tables. Multiple occurrences of the same AE in one subject during the same treatment in the trial will be counted as multiple events in the frequency counts for AEs.

An overall summary table is to be provided, presenting for each treatment sequence and all sequences pooled, the number and percentage of subjects as well as the number of events for:

- AEs
- Treatment-related AEs
- SAEs
- Treatment-related SAEs
- AEs leading to study drug interruption
- AEs leading to study drug discontinuation
- AEs leading to early study termination
- Treatment-related AEs leading to study drug discontinuation
- AESIs
- Related AESIs
- AEs leading to death

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
- Related AEs by SOC and PT
- Related SAEs by SOC and PT
- AEs leading to study drug discontinuation by SOC and PT
- Related AEs leading to study drug discontinuation by SOC and PT
- AEs by SOC, PT, and maximum severity
- AEs by SOC, PT, and strongest relationship
- AESIs by PT
- Related AESIs by PT
- Most common AEs (≥2% or more of subjects in any treatment group) by PT

Incidence for SOC will be presented by decreasing frequency overall and then alphabetically; for preferred terms, incidence will be presented by decreasing frequency overall within each SOC (if appliable) and then alphabetically.

All AEs will be listed by subject in chronological order. Separate listings will be generated for:

- AEs
- SAEs
- AEs leading to study drug discontinuation

- AEs leading to early study termination
- AESIs
- Deaths
- AEs starting in the double-blind period and leading to study drug discontinuation, early study termination or death in the open-label extension period

4.8.2 Clinical Laboratory Evaluations

Subject clinical laboratory evaluations including serum chemistry, haematology and potassium will be summarized descriptively using central laboratory.

Laboratory values will be reported in units according to the International System of Units as per Appendix 2 in the SAP.

Summaries of actual values and the change from baseline to each time point (when applicable) including last post-baseline measurement will be presented for quantitative laboratory parameters. Descriptive statistics are calculated by treatment sequence and all sequences pooled on both the actual values and the change from baseline.

Baseline is defined as the last measurement taken on or prior to the first day of open-label dosing. This will typically be the end of treatment visit for the double-blind period.

Laboratory test results will be classified according to whether the value was below (L), within (N), or above (H) the laboratory parameter reference range. A summary of shifts will compare the baseline L/N/H classification for each laboratory test to the L/N/H classification at end of open-label extension period and at last post-baseline. For serum potassium, shift table comparing the baseline L/N/H classification to each post baseline L/N/H classification (including last post-baseline) will also be provided.

All laboratory results will be listed, including data at any unscheduled visits. In addition, all abnormal (with classification of L or H) laboratory values will be presented in a separate listing.

4.8.3 12-lead Electrocardiogram (ECG) Evaluations

Summary tables for 12-lead ECG include descriptive statistics for baseline and each post baseline assessment including last post-baseline measurement during the open-label extension period. Descriptive statistics are calculated by treatment sequence and all sequences pooled on both the actual values and the change from baseline for Heart Rate, QT interval, QTcF interval, QTcB interval, RR interval, P-wave, QRS complex duration and PR interval. Overall interpretation of the 12-lead ECG readings is to be tabulated as well by treatment sequence and all sequences pooled at baseline, at end of open-label extension period and at last post-baseline assessment.

Baseline is defined as the last measurement taken on or prior to the first day of open-label dosing. This will typically be the end of treatment visit for the double-blind period.

All 12-lead ECG data will be listed in a by-subject listing and will be sorted by subject identifier and date of assessment.

4.8.4 Vital Signs Evaluations

Summary tables for vital signs include descriptive statistics for baseline and each post baseline assessment including last post-baseline measurement. Descriptive statistics are calculated by treatment sequence and all sequences pooled on both the actual values and the change from baseline for Body Temperature, Sitting Respiratory Rate, Sitting Radial Pulse Rate, Sitting Systolic Blood Pressure and Sitting Diastolic Blood Pressure.

Baseline is defined as the last measurement taken on or prior to the first day of open-label dosing. This will typically be Day 1 of the open-label extension period (prior to treatment).

All vital signs will be listed in a by-subject listing and will be sorted by subject identifier and date of assessment.

4.8.5 Other Measures

Special situations during the open-label extension period will be presented in a frequency table displaying all special situations types as per section 10.8.1 of the protocol by treatment sequence and all sequences pooled. The

special situations will be reported on a per-subject basis, i.e., this means a subject will contribute only once to the count for a given special situation category.

All special situations will be coded using MedDRA (when applicable). Coded special situations will be summarized by Primary System Organ Class and Preferred Term by treatment sequence and all sequences pooled for open-label extension period. In addition, all information regarding special situations will be listed.

In case there are 10 or less special situations in total, then special situations will be listed only.

4.9 Physical Examinations

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

4.10 Other Analyses

Pregnancy test results will be listed only.

REFERENCES

1. Guidance on Statistical Principles for Clinical Trials in Pharmaceutical Development. China Food and Drug Administration, P. R. China; Jun 2016.
2. Statistical Principles for Clinical Trials. ICH Harmonised Guideline; September 1998.

APPENDICES

Appendix 1: List of TFLs

Tables

Output No.	Titles	Population
14.1.1.1	Subject Disposition - Open-label Extension Period	Open-label Safety Analysis Set
14.1.2.1	Important Protocol Deviations - All Study Periods	Full Analysis Set
14.1.2.2	Non-Important Protocol Deviations - All Study Periods	Full Analysis Set
14.1.3.1	Demographics and Baseline Characteristics	Open-label Safety Analysis Set
14.1.3.2	Baseline Disease Characteristics	Open-label Safety Analysis Set
14.1.4.1	Medical History Recorded by System Organ Class and Preferred Term	Open-label Safety Analysis Set
14.1.5.1	Prior Medication by ATC Level 2 and ATC Level 4	Open-label Safety Analysis Set
14.1.5.2	Prior Antipruritic Medications by Ingredient	Open-label Safety Analysis Set
14.1.6.1	Study Drug Administration and Treatment Compliance - Open-label Extension Period	Open-label Safety Analysis Set
14.1.7.1	Dialysis Administration - Open-label Extension Period	Open-label Safety Analysis Set
14.2.1.1	MMRM Analysis of Change from Baseline in Total 5-D Itch Score as well as each Domain Score by Week during Open-label Extension Period (No Imputation)	Open-label Safety Analysis Set
14.2.1.2	MMRM Analysis of Change from Baseline in Total 5-D Itch Score as well as each Domain Score by Week during Overall Study (No Imputation)	Open-label Safety Analysis Set
14.2.2.1	Subjects with ≥5-point Improvement from Baseline in Total 5-D Itch Score by Week during Overall Study	Open-label Safety Analysis Set
14.2.3.1	MMRM Analysis of Change from Baseline in Total Skindex-10 Scale Score as well as each Domain Score by Week during Open-label Extension Period (No Imputation)	Open-label Safety Analysis Set
14.2.3.2	MMRM Analysis of Change from Baseline in Total Skindex-10 Scale Score as well as each Domain Score by Week during Overall Study (No Imputation)	Open-label Safety Analysis Set
14.2.4.1	Subjects with ≥15-point Improvement from Baseline in Total Skindex-10 Scale Score by Week during Overall Study	Open-label Safety Analysis Set
14.3.1.1	Overall Summary of Adverse Events during Open-label Extension Period	Open-label Safety Analysis Set
14.3.1.2	Adverse Events during Open-label Extension Period by System Organ Class and Preferred Term	Open-label Safety Analysis Set
14.3.1.3	Serious Adverse Events during Open-label Extension Period by System Organ Class and Preferred Term	Open-label Safety Analysis Set
14.3.1.4	Related Adverse Events during Open-label Extension Period by System Organ Class and Preferred Term	Open-label Safety Analysis Set
14.3.1.5	Related Serious Adverse Events during Open-label Extension Period by System Organ Class and Preferred Term	Open-label Safety Analysis Set
14.3.1.6	Adverse Events Leading to Study Drug Discontinuation during the Open-label Extension Period by System Organ Class and Preferred Term	Open-label Safety Analysis Set
14.3.1.7	Related Adverse Events Leading to Study Drug Discontinuation during the Open-label Extension Period by System Organ Class and Preferred Term	Open-label Safety Analysis Set

Output No.	Titles	Population
14.3.1.8	Adverse Events during Open-label Extension Period by System Organ Class, Preferred Term, and Maximum Severity	Open-label Safety Analysis Set
14.3.1.9	Adverse Events during the Open-label Extension Period by System Organ Class, Preferred Term, and Strongest Relationship	Open-label Safety Analysis Set
14.3.1.10	Adverse Events of Special Interest during Open-label Extension Period by Preferred Term	Open-label Safety Analysis Set
14.3.1.11	Related Adverse Events of Special Interest during Open-label Extension Period by Preferred Term	Open-label Safety Analysis Set
14.3.1.12	Most common Adverse Events (≥2% or more of subjects in any treatment sequence) during the Open-label Extension Period by Preferred Term	Open-label Safety Analysis Set
14.3.1.13	Special Situations during Open-label Extension Period by Category	Open-label Safety Analysis Set
14.3.1.14	Special Situations during Open-label Extension Period by System Organ Class and Preferred Term	Open-label Safety Analysis Set
14.3.2.1	Serious Adverse Events during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.2.2	Adverse Events Leading to Deaths during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.2.3	Adverse Events Leading to Study Drug Discontinuation during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.2.4	Adverse Events Leading to Early Study Termination during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.2.5	Adverse Events of Special Interest during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.4.1	Listing of Abnormal Laboratory Values during the Open-label Extension Period: Haematology: Haematology	Open-label Safety Analysis Set
14.3.4.2	Listing of Abnormal Laboratory Values during the Open-label Extension Period: Haematology: Serum Chemistry	Open-label Safety Analysis Set
14.3.5.1	Clinical Laboratories - Haematology: Absolute Values and Changes from Baseline during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.5.2	Clinical Laboratories - Chemistry: Absolute Values and Changes from Baseline during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.5.3	Clinical Laboratories - Chemistry Potassium: Absolute Values and Changes from Baseline during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.5.4	Clinical Laboratories - Haematology: Shifts from Baseline to the End of Open-label Extension Period by L/N/H Classification	Open-label Safety Analysis Set
14.3.5.5	Clinical Laboratories – Chemistry: Shifts from Baseline to the End of Open-label Extension Period by L/N/H Classification	Open-label Safety Analysis Set
14.3.5.6	Clinical Laboratories – Chemistry Potassium: Shifts from Baseline to the End of Open-label Extension Period by L/N/H Classification	Open-label Safety Analysis Set
14.3.6.1	ECG: Absolute Values and Changes from Baseline during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.6.2	ECG: Overall Interpretation during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.7.1	Vital Signs: Absolute Values and Changes from Baseline during the Open-label Extension Period	Open-label Safety Analysis Set
14.3.8.1	Concomitant Medication by ATC Level 2 and ATC Level 4 - Open-label Extension Period	Open-label Safety Analysis Set
14.3.8.2	Concomitant Antipruritic Medication by Ingredient - Open-label Extension Period	Open-label Safety Analysis Set

Figures

	Titles	Population
14.2.1.1	LS Mean Change from Baseline in Total 5-D Itch Score by Week during the Open-label Extension Period – Line Plot	Open-label Safety Analysis Set
14.2.1.2	LS Mean Change from Baseline in Total 5-D Itch Score by Week during Overall Study – Line Plot	Open-label Safety Analysis Set
14.2.1.3	LS Mean Change from Baseline in Total 5-D Itch Score as well as each Domain Score by Week during the Open-label Extension Period – Bar Chart	Open-label Safety Analysis Set
14.2.1.4	LS Mean Change from Baseline in Total 5-D Itch Score as well as each Domain Score by Week during Overall Study – Bar Chart	Open-label Safety Analysis Set
14.2.1.5	Percentage of Subjects with ≥5-point Improvement from Baseline in Total 5-D Itch Score by Week during Open-label Extension Period – Bar Chart	Open-label Safety Analysis Set
14.2.2.1	LS Mean Change from Baseline in Total Skindex-10 Scale Score by Week during the Open-label Extension Period – Line Plot	Open-label Safety Analysis Set
14.2.2.2	LS Mean Change from Baseline in Total Skindex-10 Scale Score by Week during Overall Study – Line Plot	Open-label Safety Analysis Set
14.2.2.3	LS Mean Change from Baseline in Total Skindex-10 Scale Score as well as each Domain Score by Week during Open-label Extension Period – Bar Chart	Open-label Safety Analysis Set
14.2.2.4	LS Mean Change from Baseline in Total Skindex-10 Scale Score as well as each Domain Score by Week during Overall Study – Bar Chart	Open-label Safety Analysis Set
14.2.2.5	Percentage of Subjects with ≥15-point Improvement from Baseline in Total Skindex-10 Scale Score by Week during Overall Study – Bar Chart	Open-label Safety Analysis Set

Listings

	Titles	Population
16.2.1.1	Subject Disposition	Open-label Safety Analysis Set
16.2.1.2	Inclusion Criteria not Met/Exclusion Criteria Met - Open-label Extension Period	All Subjects Entered Open-label Extension Period
16.2.2.1	Protocol Non-Compliance - All Study Periods	Full Analysis Set
16.2.4.1	Demographic Data	Open-label Safety Analysis Set
16.2.4.2	Baseline Disease Characteristic	Open-label Safety Analysis Set
16.2.4.3	Medical History	Open-label Safety Analysis Set
16.2.4.4	Prior and Concomitant Medications	Open-label Safety Analysis Set
16.2.4.5	Prior and Concomitant Procedures	Open-label Safety Analysis Set
16.2.5.1	Study Drug Administration Data - Open-label Extension Period	Open-label Safety Analysis Set
16.2.5.2	Study Drug Exposure, Dialysis and Compliance - Open-label Extension Period	Open-label Safety Analysis Set
16.2.5.3	Dialysis Data - Open-label Extension Period	Open-label Safety Analysis Set
16.2.5.4	Dialysis Type Adjustment - Open-label Extension Period	Open-label Safety Analysis Set
16.2.6.1	5-D Itch Scale - Open-label Extension Period	Open-label Safety Analysis Set
16.2.6.2	Skindex-10 Scale - Open-label Extension Period	Open-label Safety Analysis Set
16.2.7.1	All Adverse Events - Open-label Extension Period	Open-label Safety Analysis Set
16.2.7.2	Special Situations - Open-label Extension Period	Open-label Safety Analysis Set
16.2.7.3	Adverse Events Starting in the Double-Blind Period and Leading to Study Drug Discontinuation, Early Study Termination or Death in the Open-label Extension Period	Open-label Safety Analysis Set

	Titles	Population
16.2.8.1	Clinical Laboratory Results: Haematology - Open-label Extension Period	Open-label Safety Analysis Set
16.2.8.2	Clinical Laboratory Results: Serum Chemistry - Open-label Extension Period	Open-label Safety Analysis Set
16.2.8.3	Pregnancy Test Results (Females Only) - Open-label Extension Period	Open-label Safety Analysis Set
16.2.8.4	Comments of Clinical Laboratory Results - Open-label Extension Period	Open-label Safety Analysis Set
16.2.9.1	12-lead Electrocardiogram Results: Quantitative Assessment - Open-label Extension Period	Open-label Safety Analysis Set
16.2.9.2	12-lead Electrocardiogram Results: Qualitative assessment - Open-label Extension Period	Open-label Safety Analysis Set
16.2.9.3	Vital Signs - Open-label Extension Period	Open-label Safety Analysis Set

Appendix 2: Unit and Decimal Place

Parameters/Variables	**Unit**	**Number of decimals**
Age	years	0
Dry body weight	kg	1
Time since first diagnosis of CKD	years	1
Years on hemodialysis	years	1
Time since diagnosis of ESRD	years	1
Duration of CKD-associated pruritus	years	1
Duration of open-label treatment	days	0
Total number of doses actually received	times	0
Number of missed doses	times	0
Average dose per administration	mcg/kg	1
Average dose per administration	mcg	0
Number of extra doses	times	0
Total number of dialysis visits logged	times	0
Number of missed dialysis visits	times	0
Number of extra dialysis visits	times	0
Compliance	%	1
Albumin	g/L	1
AST/SGOT, Aspartate Aminotransferase	U/L	0
ALT/SGPT, Alanine Aminotransferase	U/L	0
Alkaline Phosphatase	U/L	0
Bilirubin (Total)	μmol/L	2
Glucose	mmol/L	2
Creatinine	μmol/L	0
Bun, Blood Urea Nitrogen	mmol/L	2
Sodium	mmol/L	0
Potassium	mmol/L	2
Chloride	mmol/L	1
Calcium	mmol/L	2
Phosphorus	mmol/L	2
Haemoglobin	g/L	0
Haematocrit	%	1
Platelet	$\times 10^9$/L	0
White Blood Cells	$\times 10^9$/L	2
Neutrophil (Absolute)	$\times 10^9$/L	2
Neutrophil %	%	1
Eosinophil (Absolute)	$\times 10^9$/L	2
Eosinophil %	%	1
Basophil (Absolute)	$\times 10^9$/L	3
Basophil %	%	1
Lymphocyte (Absolute)	$\times 10^9$/L	2
Lymphocyte %	%	1
Monocyte (Absolute)	$\times 10^9$/L	2
Monocyte %	%	1
Red Blood Cells	$\times 10^{12}$/L	2
MCV, Mean Corpuscular Volume	fL	1
MCH, Mean Corpuscular Haemoglobin	pg	1
MCHC, Mean Corpuscular Haemoglobin Concentration	g/L	0
RDW, Red Blood Cell Distribution Width	%	1
β-HCG from Serum Pregnancy Test	IU/L	3
Body temperature	C	1

Parameters/Variables	Unit	Number of decimals
Respiratory rate	breaths/min	0
Radial pulse rate	beats/min	0
Systolic blood pressure	mmHg	0
Diastolic blood pressure	mmHg	0
Heart rate	Beats/Min	0
QT Interval	msec	0
QTcF Interval	msec	0
QTcB Interval	msec	0
RR Interval	sec	1
P-wave	msec	0
QRS complex duration	msec	0
PR Interval	msec	0

Appendix 3: Listing of Laboratory Assays

Haematology:	**Serum Chemistry Panel:**
White blood cell count	Alanine aminotransferase
Red blood cell count	Albumin
Haemoglobin	Alkaline phosphatase
Haematocrit	Aspartate aminotransferase
MCV, Mean corpuscular volume	Bilirubin (total)
MCH, Mean corpuscular haemoglobin	BUN, Blood urea nitrogen
MCHC, Mean corpuscular haemoglobin concentration	Calcium
RDW, Red blood cell distribution width	Chloride
Platelet count	Creatinine
Differential white blood cell count	Glucose
Neutrophil (absolute)	Phosphorus
Neutrophil %	Potassium
Monocyte (absolute)	Sodium
Monocyte %	
Lymphocyte (absolute)	**Separate serum potassium:**
Lymphocyte %	Potassium
Eosinophil (absolute)	
Eosinophil %	**Other:**
Basophil (absolute)	Serum pregnancy test (for female subjects)
Basophil %	

Certificate Of Completion

Envelope Id: PPD
Subject: Complete with Docusign: KOR-CHINA-301 SAP OLE_V2.0.pdf
Source Envelope:
Document Pages: 36 Signatures: 5
Certificate Pages: 6 Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC+08:00) Beijing, Chongqing, Hong Kong, Urumqi

Status: Completed

Envelope Originator:
PPD
618 Jiangnan Rd Dongguan Building PPD
Binjiang District
Hangzhou, ZheJiang 310052
PPD
IP Address: PPD

Record Tracking

Status: Original
28 November 2024 | 16:29

Holder: PPD
PPD

Location: DocuSign

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 28 November 2024 | 16:31 Viewed: 28 November 2024 | 16:33 Signed: 28 November 2024 | 16:34
Electronic Record and Signature Disclosure: Accepted: 22 August 2022 | 15:50 ID: PPD Company Name: Hangzhou Tigermed Consulting Co., Ltd.		
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 28 November 2024 | 16:31 Resent: 28 November 2024 | 16:40 Viewed: 28 November 2024 | 16:47 Signed: 28 November 2024 | 16:48
Electronic Record and Signature Disclosure: Accepted: 05 May 2023 | 18:12 ID: PPD Company Name: Hangzhou Tigermed Consulting Co., Ltd.		

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): J'approuve ce document	Sent: 28 November 2024 | 16:31 Resent: 28 November 2024 | 16:40 Viewed: 28 November 2024 | 18:28 Signed: 28 November 2024 | 18:28
Electronic Record and Signature Disclosure: Accepted: 28 November 2024 | 18:28 ID: PPD Company Name: Jiaxing Tigermed Data Management Co., Ltd.		
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 28 November 2024 | 16:31 Resent: 28 November 2024 | 16:40 Viewed: 28 November 2024 | 17:24 Signed: 28 November 2024 | 17:24
Electronic Record and Signature Disclosure: Accepted: 28 November 2024 | 17:24 ID: PPD Company Name: Jiaxing Tigermed Data Management Co., Ltd.		
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 28 November 2024 | 16:31 Resent: 28 November 2024 | 16:40 Viewed: 28 November 2024 | 17:12 Signed: 28 November 2024 | 17:13
Electronic Record and Signature Disclosure: Accepted: 28 November 2024 | 17:12 ID: PPD Company Name: Jiaxing Tigermed Data Management Co., Ltd.		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	28 November 2024 | 16:31
Certified Delivered	Security Checked	28 November 2024 | 17:12
Signing Complete	Security Checked	28 November 2024 | 17:13
Completed	Security Checked	28 November 2024 | 18:28
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Jiaxing Tigermed Data Management Co., Ltd. (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Jiaxing Tigermed Data Management Co., Ltd.:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by phone call:PPD
To contact us by email send messages to: PPD

To advise Jiaxing Tigermed Data Management Co., Ltd. of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at PPD and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Jiaxing Tigermed Data Management Co., Ltd.

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to PPD and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Jiaxing Tigermed Data Management Co., Ltd.

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to PPD and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Jiaxing Tigermed Data Management Co., Ltd. as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Jiaxing Tigermed Data Management Co., Ltd. during the course of your relationship with Jiaxing Tigermed Data Management Co., Ltd..