STATISTICAL ANALYSIS PLAN (SAP) - PERIOD: DOUBLE-BLIND

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
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Sponsor:	Vifor Fresenius Medical Care Renal Pharma Ltd. Rechenstrasse 37 St. Gallen CH-9014 Switzerland
SAP Version:	Version 2.0
SAP Version Date:	12 Aug 2024
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APPROVAL SIGNATURES FOR SAP - PERIOD: DOUBLE-BLIND

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

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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
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CKD-aP	Chronic kidney disease-associated pruritus
CRO	Contract research organisation
DB-SAF	Double-blind safety analysis set
DRM	Data review meeting
ECG	Electrocardiogram
eCRF	Electronic case report form
ESRD	End stage renal disease
ET	End of treatment
FAS	Full analysis set
HD	Haemodialysis
ICF	Informed consent form
IRT	Interactive Response System
ITT	Intent-to-treat
IV	Intravenous
LS	Least squares
KOR	Kappa opioid receptor
MAR	Missing at random
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities

MI	Multiple imputation
MMRM	Mixed-effect model for repeated measures
N	Number
NRS	Numerical Rating Scale
PD	Protocol deviation
PPS	Per protocol set
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	27Jun2023	Initial version, based on protocol V 2.0, 29-Mar-2022
0.2	12Sep2023	Updated according to sponsor's comments.
0.3	18Oct2023	Updated according to sponsor's comments.
0.4	27Nov2023	Updated according to sponsor's comments.
0.5	21Dec2023	Updated according to sponsor's comments.
0.6	11Mar2024	Updated according to dry run 1 comments.
1.0	07May2024	Version 1.0 finalised
1.1	06Aug2024	Updated according to dry run 2 comments.
2.0	12Aug2024	Version 2.0 finalised

1 INTRODUCTION

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

The estimand framework included in the addendum to the ICH E9 guideline has been implemented in the SAP for the primary and secondary endpoints.

Regarding the randomisation numbers, randomisation list was not created for each stratum, instead each randomisation block is attributed to a single stratum based on data collected in electronic case report form (eCRF), i.e. the strata information from eCRF Randomisation page.

Regarding the treatment randomisation information, it will be kept confidential by the independent randomisation statistician until the data freeze for double-blind period analysis. Any changes after the data freeze and prior to database lock for the open-label analysis will be documented.

As per protocol, the duration of double-blind treatment (days) is to be calculated as (date of first dialysis after last dose) – (date of first dose) + 1. As the date of first dialysis after last dose is not collected, the duration of double-blind treatment (days) is to be calculated as (date of the last dose + 2.5) – (date of first dose) + 1.

Two additional analysis sets are added for the presentation of subject disposition and data listings: all screened set and all randomised set.

Regarding the definition of full analysis set, the criteria “Had at least 1 post-baseline assessment for the weekly mean of the daily 24-hour Worst Itching Intensity NRS (WI-NRS) score” is removed in the SAP to be aligned with the Intent-to-treat (ITT) principle.

Regarding the Mixed-effect model for repeated measures (MMRM) model of the primary endpoint, repeated measures will include values collected at the end of Weeks 1, 2, 3, 4 up to Week 12 for consistency with the secondary endpoint instead of including values collected at the end of Weeks 1, 2, 3, and 4. The primary endpoint will still be assessed at Week 4 of the double-blind period.

The protocol stipulates that the Per-Protocol Set (PPS) will be used to analyse efficacy endpoints collected during the double-blind period. The SAP clarifies that the PPS will be used for the primary efficacy analysis only.

The baseline definition for WI-NRS in the protocol specifies that 'pre-randomization' assessments collected on Day 1 will be included in the baseline calculation. This has been amended in the SAP to confirm that assessments performed on the same day as randomization (irrespective of time) can be considered as baseline, provided the assessment occurs prior to the first date/time of study drug.

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.

Subjects eligible for randomisation in the double-blind part of the study are randomised 1:1 to either difelikefalin or placebo treatment groups and receive a randomisation number. Subjects are stratified according to their use or non-use of concomitant medications to treat their itch during the week prior to

randomisation (run-in period) as well as the presence or absence of specific medical conditions. These specific medical conditions include:

- History of fall or fracture (related to fall)
- Confusional state or mental status change or altered mental status or disorientation
- Gait disturbance or movement disorder

Randomised subjects who terminate their study participation for any reason, regardless of whether the investigational product was administered or not, retain their randomisation number. The next subject is given the next randomisation number.

During the double-blind period, the investigational product is injected into the venous line of the dialysis circuit at the end of each dialysis session for 12 weeks (3 times weekly, 36 times in total). The dose of the investigational product is determined based on the subject's prescription dry body weight (i.e., the target post-dialysis weight, as determined by the patient's nephrologist or dialysis unit) at the start day of the double-blind treatment period. The first dose of investigational product is administered on Day 1, which occurs preferably on the first dialysis session of the first treatment week (i.e., Monday for subjects on a Monday-Wednesday-Friday dialysis schedule, or Tuesday for subjects on a Tuesday-Thursday-Saturday dialysis schedule).

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.

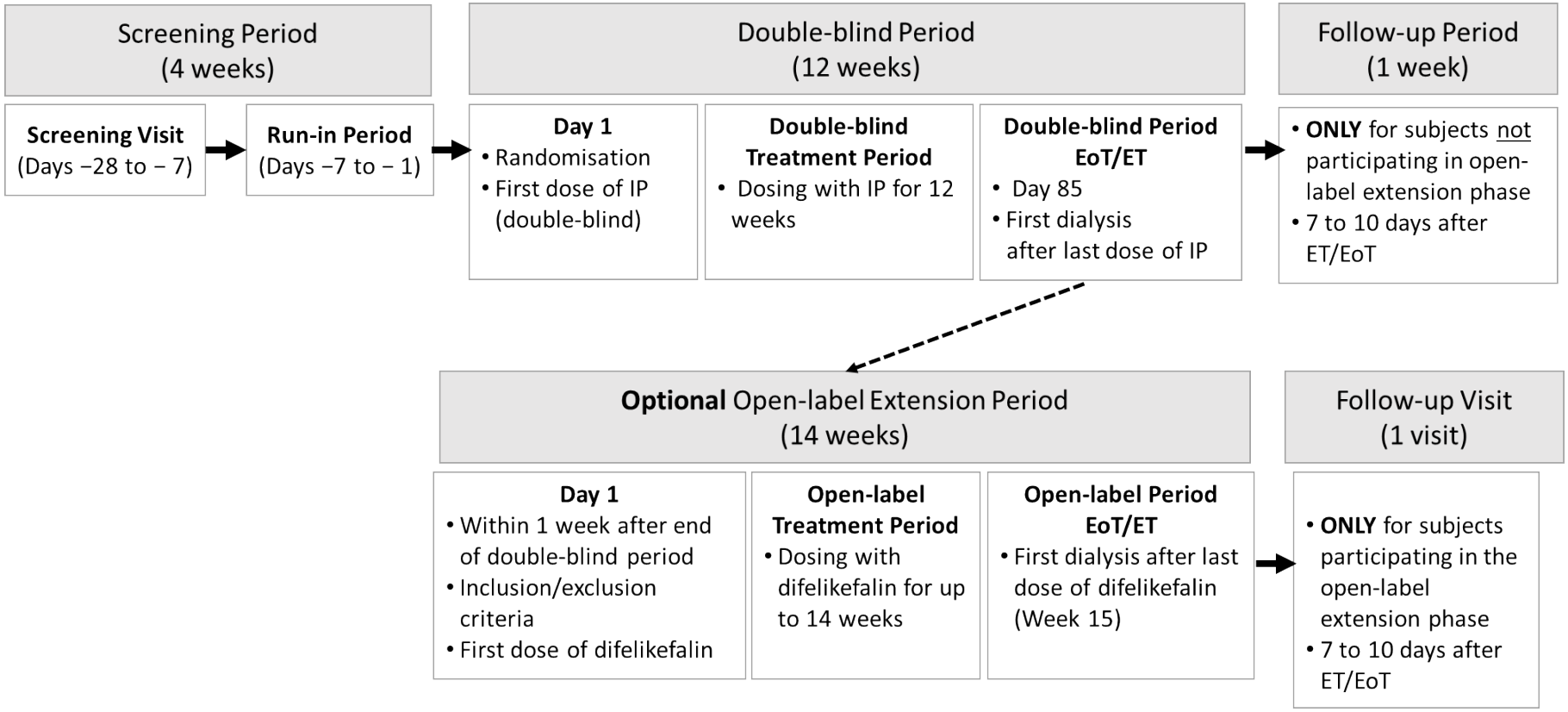
The study also includes a 1-week (1 week to 10 days) follow-up period after last administration of investigational product (end of double-blind period or end of open-label extension period or early discontinuation).

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 for the frequency and timing of the required study assessments during double-blind period.

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		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)
	Screening Visit[1]	Run-in Period[1]								
Visit Days	Day -28 to Day -7	Day -7 to Day -1	Week 1			Weeks 2 to 12			Week 13	Follow-up
Study day	-28 to -7	-7 to -1	M/Tu 1	W/Th 3	F/Sa 5	M/Tu	W/Th	F/Sa	85	Day 1 to 10 after EoT 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

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	M/Tu 3	W/Th F/Sa 5	M/Tu	W/Th	F/Sa			85	85 to 95
Concomitant medications (including antipruritic medications)[16]			X	Record on an ongoing basis							X	X
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.

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 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. Analysis of the open label extension period will be described in a separate SAP.

2.5 Randomisation and Blinding

Randomisation

All subjects enrolled must be identifiable throughout the study.

Randomisation of subjects is to be performed on Day 1 before start of treatment with study drug.

Each eligible subject is to be randomised during the double-blind period as described in Section 2.2 and Protocol Section 6.8.1.

Before the start of the study, a list of randomisation IDs is to be created and uploaded in to the Clinflash Interactive Response System (IRT) by Contract Research Organisation (CRO) independent randomisation statistician. Each randomisation block is attributed to a single stratum based on the real strata information entered in eCRF. If all subjects randomised in eCRF are within the same stratum, then all randomisation blocks are attributed to the same stratum since there is no limitation regarding the maximum number of subjects within a stratum. The randomisation list is kept strictly confidential, accessible only to authorised people, until the time of unblinding after database freeze of the double-blind period analysis data.

Blinding

During the double-blind period, study participants, Investigators, site study staff, and the Sponsor/ CRO are to be blinded to investigational product assignment.

A dummy randomisation list is put in place for the oversight and preparation of programming and statistical activities, and is to be used until the double-blind period data has been frozen and unblinded. All statistical analyses prior double-blind period database freeze (e.g. Dry run, Data review meeting [DRM] material) are to be performed by CRO team using the dummy randomisation list. The Sponsor and CRO teams are to be unblinded after the double-blind period database freeze. The dummy randomisation list is to be replaced by the real randomisation list provided by the CRO randomisation statistician for the double-blind period final statistical analysis.

Clinical trial supply management staff has access to overall difelikefalin/placebo usage at a site level for oversight of investigational product stock levels.

If the Investigator or site study staff become aware of a subject's investigational product assignment, efforts should be made to not disclose treatment assignments to other study site staff, subjects, or their caregivers.

Unblinding

During the double-blind period, the study blind is to be broken for an individual subject only in the situations described in Section 6.1.1 of the protocol.

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 analysis will include only the data for the double-blind period, i.e.

1) For subjects treated in the open label extension: up to first dose of the open label extension
2) For subjects not treated in the open label extension/not entering in the open label extension: up to the date of study completion/discontinuation.

2.6 Study Endpoints

2.6.1 Primary Efficacy Endpoint

- Change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 of the double-blind period*.

*The degree of the most intense itching within a day is to be assessed using NRS scores.

2.6.2 Secondary Efficacy Endpoints

- Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 4 of the double-blind period.
- Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 8 of the double-blind period.
- Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 12 of the double-blind period.
- Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 4 of the double-blind period.
- Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 8 of the double-blind period.
- Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 12 of the double-blind period.
- Change from baseline in itch-related QoL at the end of Week 12 of the double-blind period, as assessed by the 5-D itch scale total score.
- Change from baseline in itch-related QoL at the end of Week 12 of the double-blind period, as assessed by the Skindex-10 scale total score.
- Change from baseline in the weekly mean of the 24-hour WI-NRS score at each week of the double-blind period.
- Change from baseline in itch-related QoL at each time point of the double-blind period and 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 double-blind period and open-label extension phase, as assessed by the Skindex-10 scale total score.

- Patient Global Impression of Change.

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 HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Primary endpoint

The efficacy of difelikefalin 0.5 µg/kg compared to placebo is to be evaluated based on primary efficacy endpoint, i.e., the change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 of the double-blind period.

The null hypothesis in this study is that there is no treatment difference in the primary efficacy analysis of the primary endpoint. The alternative hypothesis is that in subjects randomised to difelikefalin there is a significant treatment difference in change in itching compared to subjects randomised to placebo. The assessment is based on the mean change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 of the double-blind period.

The hypotheses that correspond to the primary analyses are:

H_0: $\mu_{Difelikefalin} - \mu_{Placebo} = 0$

H_a: $\mu_{Difelikefalin} - \mu_{Placebo} \neq 0$

Where: µ represents the mean change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 of double-blind period.

3.2 Statistical Decision Rules

Testing of the primary efficacy endpoint is 2-sided and conducted at the 5% error level. The efficacy of difelikefalin is to be declared for this study if the null hypothesis of no treatment difference in the primary efficacy analysis of the primary endpoint (change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 of double-blind period) is rejected in favour of the alternative that subjects randomised to difelikefalin experience significantly different itching compared to subjects randomised to placebo. The null hypothesis is to be rejected if the primary analysis 2-sided p value is < 0.05

Significance level is set at an alpha of 0.05 (2-sided) and no adjustment is to be made for testing multiple secondary endpoints. Some significant findings are expected to occur by chance so undue consideration should not be given to any particular significant difference. Moreover, interpretation of the results is to be based on patterns of differences and in conjunction with the results of the primary endpoint efficacy analyses.

4 ANALYSIS SETS

4.1 All Screened Set

All screened set is defined as the group of subjects who signed the informed consent.

4.2 All Randomised Set

All randomised set is defined as the group of subjects who were randomised in the double-blind period. Subjects in all randomised set are to be analysed according to their randomised treatment.

4.3 Double-blind Safety Analysis Set (DB-SAF)

The double-blind safety analysis set (DB-SAF) is defined as all subjects in the randomised analysis set who received at least 1 dose of investigational product during the double-blind period. Subjects in the DB-SAF are to be analysed according to the actual treatment received. The DB-SAF is to be used to analyse exposure data as well as all safety endpoints collected during the double-blind period.

4.4 Full Analysis Set (FAS)

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

Subjects in the FAS are to be analysed according to their randomised treatment, regardless of the actual treatment received. The FAS is to be used to analyse all efficacy endpoints collected during the double-blind period.

4.5 Per-Protocol Set (PPS)

4.5.1 Per-Protocol Set

The PPS is defined as the population of subjects excluding the following subjects from the FAS:

- Not meeting inclusion criteria or meeting exclusion criteria related to efficacy evaluation
- Missing average 24-hour weekly WI-NRS score at Week 4
- Given < 9 or > 15 doses of the study drug before Week 4 in the double-blind period
- Significant changes in the dosage and/or administration of conditionally permitted concomitant medication before end of Week 4 in the double-blind period
- Use of prohibited concomitant medications as per Section 6.8.1.1 from the protocol and/or use of phototherapy before end of Week 4 in the double-blind period that may have significant impact on efficacy
- Significant changes in the dialysis frequency or in the hemodialysis method before end of Week 4 in the double-blind period
- Any other major protocol deviation (PD) that would impact the primary efficacy outcome (see Section 4.5.2).

Subjects in the PPS are to be analysed according to their randomised treatment, regardless of the actual treatment received. The PPS is to be used to analyse the primary efficacy endpoint and is to act as a supportive analysis.

4.5.2 Protocol Deviations

The CRO is responsible for producing the PD file and for updating it periodically (formatted as an Excel file). This file includes a description of each PD and identifies clearly whether or not each deviation warrants an exclusion from a population (classification as Major/Minor). Programmable PDs and PDs identified by sites/CRO or during medical monitoring are reconciled on a regular basis by the CRO. Based on the PDs non-compliance list, the sponsor reviews and updates the file to provide the final assessment of the PDs. The PDs recorded in the file are to be used and discussed during the blind DRM to determine whether or not subjects are to be excluded from a population. A Major PD impacting the primary efficacy outcome can only be assessed if the PD is in the first 4 weeks of the study; otherwise, the PD will be set to Minor. The final decision on the assessment of PDs (for the impact on primary efficacy outcome) will be taken by the sponsor prior to database freeze and unblinding.

5 DESCRIPTION OF THE STATISTICAL ANALYSIS

This section describes the statistical analyses related to the double-blind period, the presentation of its results, and its study endpoints/measures collected and/or derived during the double-blind period and its follow-up at the time points specified in the Schedule of Events (as per Table 1 in this document).

5.1 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

5.1.1 Standard Descriptive Statistics

Continuous Variables

Unless specified otherwise, the following standard descriptive statistics will be provided for continuous variables by treatment group: 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 group: 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.

5.1.2 Definition of Baseline, Visits and Visit Windows

For any safety analysis of the double-blind period, the baseline is defined as the last available (non-missing) value (scheduled or unscheduled) before or on the same day as the first administration of the study drug during double-blind period. For any safety analysis of the double-blind period, study day 1 is defined as the day of the first study drug administration during double-blind period (as per the "Study Drug Administration-Double Blind" eCRF page).

For any efficacy analysis of the double-blind period other than the WI-NRS score, the baseline is defined as the last available (non-missing) value (scheduled or unscheduled) before or on the same day as the randomisation day or if missing as any values during Week 1 (<=Day 7). Study day 1 for any efficacy analysis of the double-blind period is defined as the day of the randomisation (as per the Randomisation eCRF page).

As a general rule for safety and efficacy related summaries (e.g., tables and figures) other than the ones related to WI-NRS score, the visit label mentioned in Table 2A will be used to present the corresponding data by study visits for double-blind period.

Table 2A: Study Visits and Planned Assessment Window for Safety Analysis and Efficacy Analysis other than the WI-NRS Score

Visit	Visit Label	Planned Target Day (Assessment Time Window) for by visit parameters
Screening (including Run-in Period)		
Week 1	Baseline	Day 1 (≤ Day 1) [a]

Visit	Visit Label	Planned Target Day (Assessment Time Window) for by visit parameters
Week 3	Double-blind end of Week 2	Day 15 (Day 8 to Day 21)
Week 5	Double-blind end of Week 4	Day 29 (Day 22 to Day 35)
Week 7	Double-blind end of Week 6	Day 43 (Day 36 to Day 49)
Week 9	Double-blind end of Week 8	Day 57 (Day 50 to Day 63)
Week 11	Double-blind end of Week 10	Day 71 (Day 64 to Day 77)
EoT (Double- Blind)	Double-blind end of Week 12	Day 85 (Day 78 to max [EoT/ET visit, 85])
	Last Post-baseline [b]	Refer to the footnote for the definition
Follow-up (Double- Blind)	Follow-up Week 1 [c]	EoT/ET visit + 7 Days ([EoT/ET visit + 1] to max [EoT/ET visit + 10, 95]))

[a] Study Day 1 for any safety analysis is defined as the day of the first study drug administration during double-blind period (as per the "Study Drug Administration-Double Blind" eCRF page). Study Day 1 for any efficacy analysis of the double-blind period other than the WI-NRS score is defined as the day of the randomisation (as per the Randomisation eCRF page) and the planned target day is Day 1 for 5-D itch scale, Skindex-10 scale.

[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 Week 1 is applicable for safety analysis only.

For WI-NRS score, the weekly mean of the 24-hour WI-NRS score will be defined as the sum of the daily WI-NRS score reported during a specific week during the double-blind period divided by the number of days with non-missing scores for that week. Study day 1 is defined as the day of the randomisation (as per the Randomisation eCRF page). For example, data collected on study days 2 to 8 is to be used to derive the weekly mean WI-NRS at Week 1, data collected on study days 9 to 15 is to be used to derive the weekly mean at Week 2, data collected on study days 16 to 22 is to be used to derive the weekly mean at Week 3, and data collected on study days 23 to 29 is to be used to derive the weekly mean at Week 4 and so on. If the daily WI-NRS is missing for >3 days during a specific week, the corresponding weekly mean WI-NRS is to be set to missing. The baseline score is calculated using all available non-missing scores collected on or before day of randomisation, and, prior to date/time of first treatment. Note, if multiple assessments are performed on the same day, these scores will be included in the mean calculation.

As a general rule for Weekly WI-NRS score related summaries (e.g., tables and figures), the visit label mentioned in Table 2B will be used to present the corresponding data by study visits.

Table 2B: Study Visits and Planned Assessment Window for Weekly WI-NRS Score

Visit	Visit Label	Assessment Time Window for WI-NRS score
Run-in Period	Baseline	Days -7 to 1 [a]
Week 1	Week 1	Days 2 to 8
Week 2	Week 2	Days 9 to 15
Week 3	Week 3	Days 16 to 22
Week 4	Week 4	Days 23 to 29
Week 5	Week 5	Days 30 to 36
Week 6	Week 6	Days 37 to 43
Week 7	Week 7	Days 44 to 50
Week 8	Week 8	Days 51 to 57
Week 9	Week 9	Days 58 to 64
Week 10	Week 10	Days 65 to 71
Week 11	Week 11	Days 72 to 78
Week 12	Week 12	Days 79 to 85

[a] Study Day 1 is defined as the day of the randomisation (as per the Randomisation eCRF page).

5.1.3 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 2A and Table 2B.

5.1.4 Treatment Start/Stop Dates

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

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

Treatment start and stop dates will not be imputed.

5.1.5 Tables and Listings Presentation

Treatment groups 'Placebo' and 'Difelikefalin' will be displayed in the summary tables and figures and a 'Total' column will be displayed for tables, when applicable. The order of the treatment groups will be as shown below.

1. Placebo
2. Difelikefalin
3. Total (if applicable)

The listings will display all the double-blind period data contained in the eCRF, as well as derived variables. When applicable listings will include the screen failure subjects collected information.

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.

5.1.6 Analysis Populations

Please refer to Section 4 for analysis set.

5.1.7 Pooling of Sites/Country

Not applicable, this study involves only China as country.

5.1.8 Analysis of Subgroups

Subgroup analysis for the primary endpoint will be conducted for the following subgroups:

1) Randomisation stratum: Use or non-use of concomitant medications to treat their itch during the week prior to randomisation (run-in period): use vs. non-use
2) Randomisation stratum: The presence or absence of specific medical conditions at baseline: presence vs. absence

3) Itch severity at baseline: moderate (WI-NRS ≥4 to <7) vs. severe (WI-NRS ≥7)

4) Dialysis type at baseline if enough data are available by dialysis type: (hemodialysis only versus any other type)

5.1.9 Methods for Handling and Imputation of Missing Data

5.1.9.1 Primary Efficacy Analysis

Primary efficacy analysis

In the primary efficacy analysis, there will be no imputation of the missing weekly mean of the daily 24-hour WI-NRS scores.

For sensitivity analyses, the missing weekly mean weekly mean of the daily 24-hour WI-NRS scores will be imputed by the methods described below.

Sensitivity 1 analysis: MAR Multiple Imputation (MI) – MMRM

Missing weekly mean WI-NRS scores are to be imputed using a multiple imputation (MI) MAR approach, assuming that subjects who do not have weekly mean WI-NRS score at a timepoint would have similar weekly mean WI-NRS scores as other subjects in their respective treatment arm who have complete data. Imputation will be performed using all available data collected at each time point between Week 1 and Week 12 of the double-blind period.

- Intermittent missing weekly mean WI-NRS scores are first to be imputed using the Markov Chain Monte Carlo method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.
- The monotone missing weekly mean WI-NRS values are then to be multiply imputed with the SAS MI procedure using the monotone regression method.
- At either stage, MI will be performed within treatment group with covariates for baseline weekly mean WI-NRS score, both randomisation stratification factors and all non-missing weekly mean WI-NRS scores for each week. Should convergence issues occur due to small cell size for the categorical covariates corresponding to strata (at either stage), those specific covariates will be removed from the model.
- 20 imputations will be performed.

For the detailed SAS code, please refer to Appendix 4 in this document.

Sensitivity 2 analysis: Placebo MI – MMRM

Missing weekly mean WI-NRS scores are to be imputed using a multiple imputation (MI) approach, assuming that subjects who do not have weekly mean WI-NRS data at a timepoint would have similar weekly mean WI-NRS scores as other subjects in the placebo arm who have complete data. Imputation will be performed using all available data collected at each time point between Week 1 and Week 12 of the double-blind period.

- Intermittent missing weekly mean WI-NRS scores will first be imputed using the Markov Chain Monte Carlo method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data. Covariates for baseline weekly mean WI-NRS score, both randomisation stratification factors and all non-missing weekly mean WI-NRS scores for each week will be included.
- The monotone missing weekly mean WI-NRS values will then be multiply imputed with the SAS MI procedure using the monotone regression method. Covariates for baseline weekly mean WI-NRS score, both randomisation stratification factors and all non-missing weekly mean WI-NRS scores for each week will be included.
- The MNAR option in Proc MI will be used with the visit values and will reference the placebo group for informing the imputation.

- At either stage, should convergence issues occur due to small cell size for the categorical covariates corresponding to strata, those specific covariates will be removed from the model.
- 20 imputations will be performed.

For the detailed SAS code, please refer to Appendix 4 in this document.

5.1.9.2 Secondary Efficacy Analysis – Proportion of subjects with weekly mean WI-NRS improvement

For the secondary efficacy analysis of the proportion of subjects achieving ≥3-point and ≥4-point improvement, respectively, from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 4, 8 and 12 of the double-blind period, missing weekly mean WI-NRS data will be imputed using MAR MI approach described in Section 5.1.9.1.

An additional analysis will be performed where subjects who discontinue study drug early will be considered non-responders (including subjects that discontinue study drug, but continue to report NRS scores). Subjects who do not discontinue treatment but have missing weekly mean WI-NRS data will be imputed via MAR MI described in Section 5.1.9.1.

5.1.9.3 Secondary Efficacy Analysis – Change from baseline in itch-related QoL (5-D itch and Skindex-10 scale) and WI-NRS score endpoints

For the secondary efficacy analysis of the change from baseline in weekly mean WI-NRS score at each week, missing data will be not imputed for the main analysis. Sensitivity analyses will be performed using the MAR MI and Placebo MI approaches described in Section 5.1.9.1.

For the secondary efficacy analysis of the change from baseline in itch-related QoL (5-D itch and Skindex-10 scale) missing data will not be imputed.

5.1.9.4 AE, diagnosis and laboratory values

No further imputations are to be performed for missing data except for AE 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.

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 year is the same as first drug administration, or if only the day is missing, and month and year are the same as first drug administration then the start date is to be replaced by the minimum between first drug administration date 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 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).

5.2 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. For the double-blind period analysis, whether a subject enters the open label period or not is collected according to the question "Will the subject enter the open-label extension" in "Confirmation to enter open label" eCRF page.

The number of subjects screened, re-screened, not randomised, randomised, treated, not treated in double-blind period are to be summarised by treatment group, when applicable, and overall. The number of subjects who completed or early discontinued from the double-blind treatment period and from the study during the double-blind period, along with the discontinuation reasons, as well as the number of subjects who entered the Open Label period are to be summarised by treatment group and overall. The following provides the definitions of the aforementioned groups:

- Screened subjects are all subjects who sign informed consent.
- Randomised subjects consist of all screened set who have a randomisation date and time
- Treated subjects are all randomised set who received at least one dose of double-blind study drug.
- Subjects who completed double-blind treatment are 1) those subjects who entered the Open Label period or 2) those subjects who did not enter the Open Label period but completed the study treatment at the end of the double-blind period.
- Subjects who discontinued double-blind treatment period prematurely are all treated subjects who discontinued the treatment prematurely during the double-blind period.
- Subjects who completed study during the double-blind treatment period are all randomised set who completed the study as per protocol while not entering the Open Label extension period.
- Subject who entered the Open Label period are all subjects randomised and confirmed as entering the Open Label extension period.

The number and percentage of subjects having at least one major PD(s) impacting the primary efficacy analysis will be summarized within each category and subcategory of deviations by treatment group and overall using the FAS.

In addition, the number of subjects in each analysis set will be tabulated by treatment group and overall as well as the number of subjects randomised by site using all randomised set. The randomisation stratification factors recorded from IRT and eCRF will be summarized by treatment group and overall using the FAS.

The following data will also be presented in the listings:

- Subject disposition data to be presented in a by-subject listing for all randomised set.
- Subjects not randomised to be presented in a by-subject listing for all screened set.
- Inclusion criteria not met/exclusion criteria met data to be presented in a by-subject listing for all randomised set.
- Comparing randomisation Stratification factors recorded on the randomisation page vs. recorded in IRT to be presented in a by-subject listing for all randomised set.
- All the protocol non-compliance data will be listed in a by-subject listing for all randomised set.
- Subject population data will be presented in a by-subject listing for all randomised set specifying subject excluded from each analysis set with the corresponding reason of exclusion.

5.3 Demographics and Baseline Subject Characteristics

Demographic and baseline disease characteristics are to be summarised descriptively by treatment group and overall for FAS and DB-SAF population and listed for all randomised set.

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); baseline prescription dry body weight (kg).

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 an abbreviation for Hemodiafiltration, and HP is an 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 5.1.9.4.

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

Comparison of the randomisation stratification factors (randomisation stratum vs. observed stratum) is to be summarised for FAS.

5.4 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions are to be summarized for FAS and DB-SAF respectively and listed for all randomised set.

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 treatment group. Text “Not Coded” will be displayed in case terms are not coded.

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, whether or not the condition is ongoing and treated.

5.5 Prior and Concomitant Medications and Procedures

5.5.1 Prior and Concomitant Medications

Prior and concomitant medications are to be summarized for FAS and DB-SAF respectively and listed for DB-SAF.

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.

A concomitant medication during double-blind period is defined as

1) For subjects who continued into the open-label extension:
    a. any medication/therapy used on or after the date of the first dose administration of investigational product of the double-blind period with the medication start date prior to the first dose administration of open label period
    b. any medication/therapy used before the date of the first dose administration of investigational product of the double-blind period and with a missing end date or with the end date on or after the date of the first dose administration of investigational product of the double-blind period.
2) For subjects who are not treated in the open-label extension period:
    a. any medication/therapy used on or after the date of the first dose administration of investigational product of the double-blind period
    b. any medication/therapy used before the date of the first dose administration of investigational product of the double-blind period and with a missing end date or with the end date on or after the date of the first dose administration of investigational product of the double-blind period

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

In addition, prior and concomitant antipruritic medications during double-blind period will be summarized separately by ingredient and by treatment group. 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 will be presented in a by-subject listing.

5.5.2 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 will be presented in a by-subject listing.

5.6 Study Drug Exposure and Compliance

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

Study drug exposure data during double-blind period will be collected on the “Study Drug Administration-Double Blind” eCRF page and the dialysis data will be collected on the “Dialysis-Double Blind” and “Dialysis Type Adjustment” eCRF page, from randomisation on Day 1 until the end of treatment. For exposure and compliance calculations, study drug end of treatment is the “Date of Last Study Drug Administration”, as collected on the eCRF page “Treatment Termination” and for dialysis, end of treatment is the visit date of the “EOT/ET (Double-Blind)” visit (all dialyses prior to this visit will be included in the exposure and compliance calculations).

For this study, the duration of double-blind period for each individual subject may be up to 12 weeks, for a total of approximately 36 doses of investigational product administered immediately following each dialysis session. The last day of the double-blind 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 double-blind treatment period is to be summarised by treatment group and by the following parameters:

- Duration of 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)
- 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 double-blind treatment period is to be summarized by treatment group and 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 entered open label period with “Yes” collected on “Confirmation to enter open label” eCRF page, number 36 (12 weeks and 3 times for each week) is assigned. For subjects who did not enter the open label period, the following steps will be applied.
- Step 2: Keep all the doses/dialyses data during double-blind period for each subject.
- Step 3: Subjects who don’t enter open label period will be checked for how far they were into the time point of the last dose/dialysis during the double-blind 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 double-blind period for each subject.
- Step 2: Determine the last time point during the double-blind period for each subject.
- Step 3: Create a dummy dataset with each time point for each subject. For subject who entered open label period, the time points in the dummy dataset will include 36 time points, from “Week 1-Scheduled First” to “Week 12-Scheduled Third”. For subject who don’t enter open label period, the time points will include from “Week 1-Scheduled First” to the last time point (Step 2).
- 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 double-blind 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 during the double-blind period 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 double-blind period will be presented in listings.

Subjects receiving study drug different than one assigned in at least one administration will be presented in a listing.

5.7 Efficacy Analyses

5.7.1 Primary Efficacy Analysis

Primary Estimand

The primary clinical question of interest is:

What is the difference in the change from baseline to Week 4 (Days 23 to 29) of the double-blind period in the weekly mean of the daily 24-hour WI-NRS score regardless of early treatment discontinuation, regardless of significant changes to the dosage and/or administration of conditionally permitted concomitant medication, regardless of significant changes in the dialysis frequency or in the hemodialysis method, and regardless of the use of prohibited concomitant medications and/or use of phototherapy. The definition of the weekly mean of the 24-hour WI-NRS score is mentioned in SAP Section 5.1.2.

- Target population: Chinese participants with CKD on HD and with moderate-to-severe pruritus.
- Endpoint: Change from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 4 of the double-blind period
- Treatment condition: Difelikefalin 0.5 µg/kg or Placebo administered by IV bolus injection within 15 minutes following the end of the dialysis 3 times weekly or up to 4 times weekly in exceptional cases where an extra fourth dialysis session is required within the week
- Population-level summary: difference in Means between treatment groups in weekly mean of the daily 24-hour WI-NRS score change from baseline to Week 4

- The following intercurrent events are of interest for the primary estimand:
  1) Use of prohibited concomitant medications as per section 6.8.1.1 from the protocol and/or use of phototherapy that may have significant impact on efficacy
  2) Significant changes in the dosage and/or administration of conditionally permitted concomitant medication identified by medical review of the PD list prior to unblinding
  3) Significant changes in the dialysis frequency or in the hemodialysis method identified by medical review of the PD list prior to unblinding
  4) Early discontinuation of study treatment
- The intercurrent events 1 to 4 will be addressed using the treatment policy strategy. The number and percentage of subjects having at least one intercurrent event by Week 4 will be provided for each category by treatment group and overall for the FAS

Estimator

All data points will be included in the analysis regardless of the intercurrent events. This means that all available weekly mean of the daily 24-hour WI-NRS score will be used, i.e. including WI-NRS score collected after the intercurrent events. Missing weekly mean WI-NRS score will not be imputed assuming they are missing at random per MMRM model.

Treatment groups will be compared using the Least Square means of change from baseline to Week 4 in the weekly mean of the daily 24-hour WI-NRS score estimated using a MMRM that includes treatment, week, and treatment-by-week interaction as fixed effects; baseline weekly mean WI-NRS score, use of prior anti-itch medication and presence of specific medical conditions as covariates. Repeated measures will include values collected at Weeks 1, 2, 3, 4, until 12. 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. The difference between treatment groups (difelikefalin minus placebo) in the estimated Least Square mean change from baseline to week 4 will be presented with its 2-sided confidence interval (CI) as well as the p-value which will be calculated from the model. The statistical hypothesis to be tested are defined in Section 3.1.

The FAS will be used as the primary population for the analysis of the primary efficacy endpoint as well as for its sensitivity analyses. The analyses will be repeated using the PPS as a secondary population.

The MMRM model will be implemented through PROC MIXED in SAS. For the detailed SAS code, please refer to Appendix 4 in this document.

Subgroup Analyses

The analysis for the primary efficacy endpoint will be conducted for the FAS on the subgroups described in Section 5.1.8.

Sensitivity Analyses

Missing data will be imputed as described in Section 5.1.9.1 using:

- Sensitivity analysis 1: MAR MI
- Sensitivity analysis 2: Placebo MI

For each imputed dataset, the same MMRM model as the one for the primary efficacy analysis will be used. Results of the MMRM model on the multiply imputed data sets will be summarized using Rubin's rule.

5.7.2 Secondary Efficacy Analysis

Secondary and other efficacy endpoints will be analysed using the FAS. Significance level is set at an alpha of 0.05 (2-sided) and no adjustment will be made for testing multiple secondary endpoints as per Section 3.2. All questionnaire data will be listed in a by-subject listing.

5.7.2.1 Proportion of subjects with WI-NRS improvement

- Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 4 of the double-blind period.
- Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 8 of the double-blind period.
- Proportion of subjects achieving ≥3-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 12 of the double-blind period.
- Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 4 of the double-blind period.
- Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 8 of the double-blind period.
- Proportion of subjects achieving ≥4-point improvement from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 12 of the double-blind period.

Estimand

The secondary clinical questions of interest are:

What is the odds ratio for achieving ≥3-point improvement and ≥4-point improvement, respectively, from baseline at Week 4, 8 and 12 of the double-blind period with respect to the weekly mean of the daily 24-hour WI-NRS regardless of early treatment discontinuation, regardless of significant changes to the dosage and/or administration of conditionally permitted concomitant medication, regardless of significant changes in the dialysis frequency or in the hemodialysis method, and regardless of the use of prohibited concomitant medications and/or use of phototherapy.

- Target population: Chinese participants with CKD on HD and with moderate-to-severe pruritus.
- Endpoints: secondary endpoints listed as above
- Treatment condition: Difelikefalin 0.5 μg/kg or Placebo administered by IV bolus injection within 15 minutes following the end of the dialysis 3 times weekly or up to 4 times weekly in exceptional cases where an extra fourth dialysis session is required within the week regardless of early treatment discontinuation.
- Population-level summary: Odds ratios at Week 4, 8 and 12 of the double-blind period.
- The following intercurrent events are of interest for the primary estimand:
  1) Use of prohibited concomitant medications as per section 6.8.1.1 from the protocol and/or use of phototherapy that may have significant impact on efficacy
  2) Significant changes in the dosage and/or administration of conditionally permitted concomitant medication identified by medical review of the PD list prior to unblinding
  3) Significant changes in the dialysis frequency or in the hemodialysis method as identified by medical review of the PD list prior to unblinding
  4) Early discontinuation of study treatment
- The intercurrent events 1 to 4 will be addressed using the treatment policy strategy. The number and percentage of subjects having at least one intercurrent event by Week 12 will be provided for each category by treatment group and overall for the FAS.

Estimator

All data points will be included in the analysis regardless of the intercurrent events. This means that all available weekly mean of the daily 24-hour WI-NRS score will be used, i.e. including WI-NRS score collected after the intercurrent events.

All missing weekly mean WI-NRS score will be imputed using a MI MAR approach, i.e. assuming that subjects with missing data would have similar weekly mean WI-NRS score as other subjects in their respective treatment arm that have complete data as described in Section 5.1.9.2.

After imputation of missing data, the proportion of subjects who have an improvement from baseline with respect to the weekly mean WI-NRS score will be calculated for each imputed dataset. Differences between difelikefalin and placebo will be compared using odds ratio (taking the placebo treatment group as a reference) from a logistic regression model, containing terms for treatment group, baseline weekly mean WI-NRS score, use of anti-itch medication during the week prior to randomization, and presence of specific medical conditions. Results of the logistic regression on the multiply imputed data sets will be summarized using Rubin's rule. The odds ratio and its 2-sided CI will be provided as well as the p-value from the model.

The observed number and proportion of subjects achieving ≥3-point and ≥4-point improvement, respectively, among the non-imputed data will be reported along with the imputed data logistic regression model-based estimates of the proportions of responders (as defined above) with their 2-sided 95% CIs. Bar charts will also be presented for the model-based estimates of the proportion of responders.

Supplemental Estimand

The corresponding clinical questions of interest are:

What is the odds ratio for achieving ≥3-point improvement and ≥4-point improvement, respectively, from baseline at Week 4, 8 and 12 of the double-blind period with respect to the weekly mean of the daily 24-hour WI-NRS regardless of significant changes to the dosage and/or administration of conditionally permitted concomitant medication, regardless of significant changes in the dialysis frequency or in the hemodialysis method, and regardless of the use of prohibited concomitant medications and/or use of phototherapy and with early treatment discontinuation as a failure.

- Target population: Chinese participants with CKD on HD and with moderate-to-severe pruritus.
- Endpoints: secondary endpoints listed as above
- Treatment condition: Difelikefalin 0.5 µg/kg or Placebo administered by IV bolus injection within 15 minutes following the end of the dialysis 3 times weekly or up to 4 times weekly in exceptional cases where an extra fourth dialysis session.
- Population-level summary: Odds ratios at Week 4, 8 and 12 of the double-blind period
- Intercurrent events:
    1) Use of prohibited concomitant medications as per section 6.8.1.1 from the protocol and/or use of phototherapy that may have significant impact on efficacy
    2) Significant changes in the dosage and/or administration of conditionally permitted concomitant medication as identified by medical review of the PD list prior to unblinding
    3) Significant changes in the dialysis frequency or in the hemodialysis method as identified by medical review of the PD list prior to unblinding
    4) Early discontinuation of study treatment
- The intercurrent events 1 to 3 will be addressed using the treatment policy strategy. The intercurrent event 4 will be addressed using the composite variable strategy, i.e. early treatment discontinuation would be considered as a failure.

Estimator

The estimator will be similar to the one from first estimand. However, the subjects who discontinue study drug early will be considered non-responders (including subjects that discontinue study drug, but continue to report NRS scores; data on or after study drug discontinuation date will be imputed as non-responder). Subjects who do not discontinue treatment but have missing weekly mean WI-NRS data will be imputed via MAR MI described in Section 5.1.9.1.

5.7.2.2 Change from baseline in itch-related QoL

- Change from baseline in itch-related QoL at the end of Week 12 of the double-blind period, as assessed by the 5-D itch scale total score.
- Change from baseline in itch-related QoL at the end of Week 12 of the double-blind period, as assessed by the Skindex-10 scale total score.
- Change from baseline in itch-related QoL at each time point of the double-blind period, as assessed by the 5-D itch scale total score.
- Change from baseline in itch-related QoL at each time point of the double-blind period, as assessed by the Skindex-10 scale total score.

5-D Itch Scale

The 5-D Itch Scale was developed as a brief but 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 achieved 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 achieved 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 is present for disability will be used for that domain.

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 estimands for the 5-D Itch and Skindex-10 scales are similar to the one from the primary efficacy analysis. MMRM analyses described in Section 5.7.1 will be repeated for the total scores and domains. Line plots for the least square mean and mean change from baseline in total scores will be presented over time. Bar charts of the least square mean change from baseline in total scores and domains at Week 12 will also be provided.

5.7.2.3 Change from baseline in weekly mean WI-NRS

- Change from baseline in the weekly mean of the 24-hour WI-NRS score at each week of the double-blind period.

The estimand for the change from baseline in weekly mean WI-NRS score at each week is similar to the one from the primary efficacy analysis. MMRM analyses described in Section 5.7.1 will be repeated and results will be presented for each week of the double-blind period. Sensitivity analyses with missing data imputed using MAR MI and Placebo MI as described in Section 5.1.9.1 will also be performed.

Line plots for the least square mean change from baseline in weekly mean WI-NRS will be presented over time for all analysis. Line plots for the least square mean over time will be presented for the analysis without imputation only.

5.7.2.4 Patient global impression endpoint

- Patient Global Impression of Change at the end of Week 12 of the double-blind period/end of double-blind.

Estimand

The corresponding clinical question of interest is:

What is the odds ratio in the proportion of subjects achieving “Very much improved” or “Much Improved” at the end of Week 12 of the double-blind period assessed by the Patient Global Impression of Change regardless of early treatment discontinuation, regardless of significant changes to the dosage and/or administration of conditionally permitted concomitant medication, regardless of significant changes in the dialysis frequency or in the hemodialysis method, and regardless of the use of prohibited concomitant medications and/or use of phototherapy.

- Target population: Chinese participants with CKD on HD and with moderate-to-severe pruritus.
- Endpoints: The proportion of subjects achieving “Very much improved” or “Much Improved” at the end of Week 12 of the double-blind period/end of double-blind.
- Treatment condition: Difelikefalin 0.5 µg/kg or Placebo administered by IV bolus injection within 15 minutes following the end of the dialysis 3 times weekly or up to 4 times weekly in exceptional cases where an extra fourth dialysis session is required within the week.
- Population-level summary: Odds ratio at the end of Week 12 of the double-blind period.
- The following intercurrent events are of interest for the primary estimand:
    1) Use of prohibited concomitant medications as per section 6.8.1.1 from the protocol and/or use of phototherapy that may have significant impact on efficacy
    2) Significant changes in the dosage and/or administration of conditionally permitted concomitant medication as identified by medical review of the PD list prior to unblinding
    3) Significant changes in the dialysis frequency or in the hemodialysis method as identified by medical review of the PD list prior to unblinding
    4) Early discontinuation of study treatment

- The intercurrent events 1 to 4 will be addressed using the treatment policy strategy.

Estimator

All data points will be included in the analysis regardless of the intercurrent events. This means that all available patient global impression of change data will be used. Missing patient global impression of change data will not be imputed.

For the patient global impression of change collected in eCRF page “Patient Global Impression of Change”, the number and percentage of subjects for each response (“Very Much Improved”, “Much Improved”, “Minimally Improved”, “No Change”, “Minimally Worse”, “Much Worse”, and “Very Much Worse”) will be reported as well as the count of subjects with missing values.

The number and percentage of subjects who reported their itch condition in term of patient global impression of change as “Very much improved” or “Much Improved” at the end of Week 12 of the double-blind period will be reported together. The Mantel-Haenszel estimate, adjusting for the randomisation stratification variables (use of prior anti-itch medication, presence of specific medical conditions), of common odds ratio with its 2-sided 95% CI and Cochran-Mantel-Haenszel (CMH) test p-value will be reported for treatment comparison. Additionally, the 2-sided exact Clopper Pearson 95% CI for the proportion of subjects who rate their itch condition as “Very much improved” or “Much Improved” will be presented.

The FAS will be used as the primary population for the analysis of the secondary efficacy endpoint. Bar charts will be provided for the percentage of responders (“Very much improved” or “Much Improved”).

The CMH test will be implemented through PROC FREQ in SAS. For the detailed SAS code, please refer to Appendix 4 in this document.

5.8 Safety Analyses

All safety analyses are to be performed by treatment group using the double-blind safety analysis set and are to be descriptive. Missing values will not be imputed unless stated otherwise, please refer to Section 5.1.9.3.

5.8.1 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 5.1.9.4.

Adverse Event Definitions

1) An AE is defined as any event:
   - With an onset date greater than the first dose date of the investigational product in the double-blind period for subjects who do not enter the open-label extension period.
   - With an onset date greater than the first dose date of the investigational product in the double-blind period up to the first dose of difelikefalin in the open-label extension period for subjects who continue into the open-label extension period.
2) A pre-treatment AE is defined as any event that has an onset before the first investigational product administration.
3) For events starting exactly on the first dose date of the investigational product in the double-blind period, the classification as AE or pre-treatment AE is to be done based on the investigator judgment as collected in the eCRF. If this information is missing, the event is to be considered as an AE.

AEs will be presented in summary tables. Pre-treatment AEs will not be included in any summary tables.

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 group. 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 group, the number and percentage of subjects as well as the number of events for:

- AEs
- Related AEs
- SAEs
- Related SAEs
- AEs leading to study drug interruption
- AEs leading to study drug discontinuation
- AEs leading to early study termination
- 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
- 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:

- Pre-treatment AEs
- AEs
- SAEs
- AEs leading to study drug discontinuation
- AEs leading to early study termination
- AESIs
- Deaths

5.8.2 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 group on both the actual values and the change from baseline.

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 double-blind treatment 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.

5.8.3 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. Descriptive statistics are calculated by treatment group 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 group at baseline, at end of double-blind treatment and at last post-baseline assessment.

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

5.8.4 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 group 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.

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

5.8.5 Other Measures

Special situations during double-blind treatment period will be presented in a frequency table displaying all special situations types as per section 10.8.1 of the protocol by treatment group. 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 group for double-blind 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.

5.9 Physical Examinations

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

5.10 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.
3. Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials. ICH Harmonised Guideline; 20 Nov 2019.

APPENDICES

Appendix 1: List of TFLs

Tables

Output No.	Titles	Population
14.1.1.1	Subject Disposition - Double-blind Period	All Screened Set
14.1.1.2	Summary of Analysis Populations - Double-blind Period	All Randomised Set
14.1.1.3	Subject Randomised by Site	All Randomised Set
14.1.2.1	Major Protocol Deviations - Double-blind Period	Full Analysis Set
14.1.3.1.1	Demographics and Baseline Characteristics - Double-blind Period	Full Analysis Set
14.1.3.1.2	Demographics and Baseline Characteristics - Double-blind Period	Double-blind Safety Analysis Set
14.1.3.2.1	Baseline Disease Characteristics - Double-blind Period	Full Analysis Set
14.1.3.2.2	Baseline Disease Characteristics - Double-blind Period	Double-blind Safety Analysis Set
14.1.3.3	Comparison of Randomisation Stratification Factors (Randomisation Stratum vs. Observed Stratum)	Full Analysis Set
14.1.4.1	Medical History Recorded by System Organ Class and Preferred Term - Double-blind Period	Full Analysis Set
14.1.4.2	Medical History Recorded by System Organ Class and Preferred Term - Double-blind Period	Double-blind Safety Analysis Set
14.1.5.1.1	Prior Medication by ATC Level 2 and ATC Level 4 - Double-blind Period	Full Analysis Set
14.1.5.1.2	Prior Medication by ATC Level 2 and ATC Level 4 - Double-blind Period	Double-blind Safety Analysis Set
14.1.5.2.1	Prior Antipruritic Medications by Ingredient	Full Analysis Set
14.1.5.2.2	Prior Antipruritic Medications by Ingredient	Double-blind Safety Analysis Set
14.1.6.1	Study Drug Administration and Treatment Compliance - Double-blind Period	Double-blind Safety Analysis Set
14.1.7.1	Dialysis Administration during the Double-blind Period	Double-blind Safety Analysis Set
14.2.1.1.1	Primary Efficacy Endpoint: MMRM Analysis of Change from Baseline to Week 4 of the Double-blind Period in the Weekly Mean of the Daily 24-hour WI-NRS Score (No Imputation)	Full Analysis Set
14.2.1.1.2	Primary Efficacy Endpoint: MMRM Analysis of Change from Baseline to Week 4 of the Double-blind Period in the Weekly Mean of the Daily 24-hour WI-NRS Score (No Imputation)	Per-Protocol Set
14.2.1.1.3	Primary Efficacy Endpoint: MMRM Analysis of Change from Baseline to Week 4 of the Double-blind Period in the Weekly Mean of the Daily 24-hour WI-NRS Score by subgroups (No Imputation)	Full Analysis Set
14.2.1.1.4	Summary of Intercurrent Events by Week 4 - Double-blind Period	Full Analysis Set
14.2.1.2	Primary Efficacy Endpoint – Sensitivity Analysis 1: MMRM Analysis of Change from Baseline to Week 4 of the Double-blind Period in the Weekly Mean of the Daily 24-hour WI-NRS Score (Multiple Imputation with MAR Assumption)	Full Analysis Set
14.2.1.3	Primary Efficacy Endpoint - Sensitivity Analysis 2: MMRM Analysis of Change from Baseline to Week 4 of the Double-blind Period in the Weekly Mean of the Daily 24-hour WI-NRS Score (Placebo Multiple Imputation with MNAR Assumption)	Full Analysis Set

Output No.	Titles	Population
14.2.2.1.1	Secondary Efficacy Analysis: Subjects with ≥3-point Improvement from Baseline by Week with respect to the Weekly Mean of the Daily 24-hour WI-NRS in the Double-blind Period - Logistic Regression Model (Multiple Imputation with MAR Assumption)	Full Analysis Set
14.2.2.1.2	Secondary Efficacy Analysis - Supplemental Analysis: Subjects with ≥3-point Improvement from Baseline by Week with respect to the Weekly Mean of the Daily 24-hour WI-NRS in the Double-blind Period - Logistic Regression Model (Early Discontinuation as Non-responders)	Full Analysis Set
14.2.2.2.1	Secondary Efficacy Analysis: Subjects with ≥4-point Improvement from Baseline by Week with respect to the Weekly Mean of the Daily 24-hour WI-NRS in the Double-blind Period - Logistic Regression Model (Multiple Imputation with MAR Assumption)	Full Analysis Set
14.2.2.2.2	Secondary Efficacy Analysis - Supplemental Analysis: Subjects with ≥4-point Improvement from Baseline by Week with respect to the Weekly Mean of the Daily 24-hour WI-NRS in the Double-blind Period - Logistic Regression Model (Early Discontinuation as Non-responders)	Full Analysis Set
14.2.2.3.1	Summary of Intercurrent Events by Week 12 - Double-blind Period	Full Analysis Set
14.2.3.1.1	Secondary Efficacy Analysis: MMRM Analysis of Change from Baseline in Total 5-D Itch Score as well as each Domain Score by Week of the Double-blind Period (No Imputation)	Full Analysis Set
14.2.4.1.1	Secondary Efficacy Analysis: MMRM Analysis of Change from Baseline in the Skindex-10 Scale Total Score as well as each Domain Score by Week of the Double-blind Period (No Imputation)	Full Analysis Set
14.2.5.1.1	Secondary Efficacy Analysis: Change from Baseline at Each Time Point of the Double-blind Period in the Weekly Mean of the 24-hour WI-NRS Score (No Imputation)	Full Analysis Set
14.2.5.1.2	Secondary Efficacy Analysis: Change from Baseline at Each Time Point of the Double-blind Period in the Weekly Mean of the 24-hour WI-NRS Score (Multiple Imputation with MAR Assumption)	Full Analysis Set
14.2.5.1.3	Secondary Efficacy Analysis: Change from Baseline at Each Time Point of the Double-blind Period in the Weekly Mean of the 24-hour WI-NRS Score (Placebo Multiple Imputation)	Full Analysis Set
14.2.6.1	Secondary Efficacy Analysis: Summary of Patient Global Impression of Change at the end of Week 12 of the Double-blind Period (No Imputation)	Full Analysis Set
14.3.1.1	Overall Summary of Adverse Events during Double-blind Period by Treatment Group	Double-blind Safety Analysis Set
14.3.1.2	Adverse Events during Double-blind Period by System Organ Class and Preferred Term	Double-blind Safety Analysis Set
14.3.1.3	Serious Adverse Events during Double-blind Period by System Organ Class and Preferred Term	Double-blind Safety Analysis Set
14.3.1.4	Related Adverse Events during Double-blind Period by System Organ Class and Preferred Term	Double-blind Safety Analysis Set
14.3.1.5	Related Serious Adverse Events during Double-blind Period by System Organ Class and Preferred Term	Double-blind Safety Analysis Set

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

Output No.	Titles	Population
14.3.8.1.2	Concomitant Medication by ATC Level 2 and ATC Level 4 - Double-blind Period	Double-blind Safety Analysis Set
14.3.8.2.1	Concomitant Antipruritic Medication by Ingredient - Double-blind Period	Full Analysis Set
14.3.8.2.2	Concomitant Antipruritic Medication by Ingredient - Double-blind Period	Double-blind Safety Analysis Set

Figures

	Titles	Population
14.2.2.1.1	Secondary Efficacy Analysis: LS Mean Change from Baseline in Worst Itching Intensity NRS by Week during the Double-blind Period (No Imputation) – Line Plot	Full Analysis Set
14.2.2.1.2	Secondary Efficacy Analysis: LS Mean Change from Baseline in Worst Itching Intensity NRS by Week during the Double-blind Period (Multiple Imputation with MAR Assumption) – Line Plot	Full Analysis Set
14.2.2.1.3	Secondary Efficacy Analysis: LS Mean Change from Baseline in Worst Itching Intensity NRS by Week during the Double-blind Period (Placebo Multiple Imputation with MNAR Assumption) – Line Plot	Full Analysis Set
14.2.2.1.4	Secondary Efficacy Analysis: Mean Value of Worst Itching Intensity NRS by Week during the Double-blind Period (No Imputation) – Line Plot	Full Analysis Set
14.2.2.2.1	Secondary Efficacy Analysis: Proportion of Subjects with ≥3-Point Improvement with Respect to the Worst Itching Intensity NRS Score by Week during the Double-blind Period (Multiple Imputation with MAR Assumption)– Bar Chart	Full Analysis Set
14.2.2.2.2	Secondary Efficacy Analysis: Proportion of Subjects with ≥4-Point Improvement with Respect to the Worst Itching Intensity NRS Score by Week during the Double-blind Period (Multiple Imputation with MAR Assumption)– Bar Chart	Full Analysis Set
14.2.2.3.1	Secondary Efficacy Analysis: LS Mean Change from Baseline in 5-D Itch Total Score by Week during the Double-blind Period (No Imputation) – Line Plot	Full Analysis Set
14.2.2.3.2	Secondary Efficacy Analysis: Mean Value of 5-D Itch Total Score by Week during the Double-blind Period (No Imputation) – Line Plot	Full Analysis Set
14.2.2.3.3	Secondary Efficacy Analysis: LS Mean Change from Baseline in 5-D Itch Domain and Total Scores at Week 12 during the Double-blind Period (No Imputation) – Bar Chart	Full Analysis Set
14.2.2.4.1	Secondary Efficacy Analysis: LS Mean Change from Baseline in Skindex-10 Total Score by Week during the Double-blind Period (No Imputation) – Line Plot	Full Analysis Set
14.2.2.4.2	Secondary Efficacy Analysis: Mean Value of Skindex-10 Total Score by Week during the Double-blind Period (No Imputation) – Line Plot	Full Analysis Set
14.2.2.4.3	Secondary Efficacy Analysis: LS Mean Change from Baseline in Skindex-10 Scale Domain and Total Scores at Week 12 during the Double-blind Period (No Imputation) – Bar Chart	Full Analysis Set
14.2.2.5.1	Secondary Efficacy Analysis: Percent of Responders in Patient Global Impression of Change at the end of Week 12 of the Double-blind Period (No Imputation) – Bar Chart	Full Analysis Set

Listings

	Titles	Population
16.1.6.1	Subjects Receiving Test Drug(s)/Investigational Product(s) and Drug Dispensation Details	All Randomised Set
16.1.7.1	Subject Randomisation	All Randomised Set
16.2.1.1	Subject Disposition	All Randomised Set
16.2.1.2	Subjects Not Randomised	All Screened Set
16.2.1.3	Inclusion Criteria not Met/Exclusion Criteria Met	All Randomised Set
16.2.1.4	Subjects with Non-matching Planned and Actual Randomisation Stratification	All Randomised Set
16.2.2.1	Protocol Non-Compliance	All Randomised Set
16.2.3.1	Subject Population	All Randomised Set
16.2.4.1	Demographic Data	All Randomised Set
16.2.4.2	Baseline Disease Characteristics	All Randomised Set
16.2.4.3	Subgroups	All Randomised Set
16.2.4.4	Medical History	All Randomised Set
16.2.4.5	Prior and Concomitant Medications	Double-blind Safety Analysis Set
16.2.4.6	Prior and Concomitant Procedures	Double-blind Safety Analysis Set
16.2.5.1	Study Drug Administration Data during Double-blind Period	Double-blind Safety Analysis Set
16.2.5.2	Study Drug Exposure, Dialysis and Compliance during Double-blind Period	Double-blind Safety Analysis Set
16.2.5.3	Subjects Receiving Study Drug Different than the One Assigned in at Least One of the Administration	Double-blind Safety Analysis Set
16.2.5.4	Dialysis Data during Double-blind Period	Double-blind Safety Analysis Set
16.2.5.5	Dialysis Type Adjustment during Double-blind Period	Double-blind Safety Analysis Set
16.2.6.1	Worst Itching Intensity NRS during the Double-blind Period	Full Analysis Set
16.2.6.2	Intercurrent Events (by Week 4 and Week 12)	Full Analysis Set
16.2.6.3	Skindex-10 Scale during the Double-blind Period	Full Analysis Set
16.2.6.4	5-D Itch Scale during the Double-blind Period	Full Analysis Set
16.2.6.5	Patient Global Impression of Change during the Double-blind Period	Full Analysis Set
16.2.7.1	All Adverse Events during the Double-blind Period	Double-blind Safety Analysis Set
16.2.7.2	All Pre-treatment Adverse Events	Double-blind Safety Analysis Set
16.2.7.3	Special Situations during the Double-blind Period	Double-blind Safety Analysis Set
16.2.8.1	Clinical Laboratory Results during the Double-blind Period: Haematology	Double-blind Safety Analysis Set
16.2.8.2	Clinical Laboratory Results during the Double-blind Period: Serum Chemistry	Double-blind Safety Analysis Set
16.2.8.3	Pregnancy Test Results during the Double-blind Period (Females Only)	Double-blind Safety Analysis Set
16.2.8.4	Comments of Clinical Laboratory Results during the Double-blind Period	Double-blind Safety Analysis Set
16.2.9.1	12-lead Electrocardiogram Results during the Double-blind Period: Quantitative Assessment	Double-blind Safety Analysis Set
16.2.9.2	12-lead Electrocardiogram Results during the Double-blind Period: Qualitative assessment	Double-blind Safety Analysis Set
16.2.9.3	Vital Signs during the Double-blind Period	Double-blind 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 double-blind 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
	Chloride
RDW, Red blood cell distribution width	Creatinine
Platelet count	Glucose
Differential white blood cell count	Phosphorus
Neutrophil (absolute)	Potassium
Neutrophil %	Sodium
Monocyte (absolute)	
Monocyte %	**Separate serum potassium:**
Lymphocyte (absolute)	Potassium
Lymphocyte %	
Eosinophil (absolute)	**Other:**
Eosinophil %	Serum pregnancy test (for female subjects)
Basophil (absolute)	
Basophil %	

Appendix 4: SAS code

1. SAS code for MMRM

ods output LSMeans = lsmeans

Diffs = Diffs;

proc mixed data=<data> alpha=<0.05>;

class <treatment code>(ref="placebo") <visit> <use of prior anti-itch medication (yes/no)> <presence of specific medical conditions (yes/no)>;

model <change from baseline in the weekly mean of the daily 24-hour WI-NRS score> = <treatment code> <visit> <treatment code><visit> <use of prior anti-itch medication (yes/no)> <presence of specific medical conditions (yes/no)> <baseline WI-NRS score> / DDFM = KENWARDROGER2;*

repeated <visit> / subject=<subjid> type=<un>;

lsmeans <visit><treatment code> / diff cl alpha=<0.05>;*

run;

ods output close;

In the above sample SAS code, type=UN (Unstructured) will be changed to type = CS (Compound Symmetry) in the situation that the above model does not converge.

•

2. SAS code for Multiple Imputation (MI) – MMRM

****Imputations will be performed separately for each treatment group ***;*

****Placebo***;*

****The first stage of imputation will create monotone missing data using MCMC and the following code;*

proc mi data = <indata> nimpute=20 MINMAXITER=1000000 seed=905682 MAXIMUM=10 MINIMUM=0 out=<outdata1>;

mcmc chain=multiple initial=EM (CONVERGE=0.001 MAXITER=100000) NBITER=500 NITER=100 impute=monotone displayinit;

var <use of prior anti-itch medication (1 for yes/ 0 for no)> <presence of specific medical conditions (1 for yes/ 0 for no)> <baseline> <week1> <week2> <week3> <week4>… <week12>;

run;

****Using the output data, imputed data following the last non-missing will be reset to missing so that only intermittent values are imputed in this first pass;*

proc mi data = <outdata1> nimpute=1 MINMAXITER=1000000 seed=176104 MAXIMUM=10 MINIMUM=0 out=<outdata2>;

by _Imputation_;

monotone reg;

var <use of prior anti-itch medication (1 for yes/ 0 for no)> <presence of specific medical conditions (1 for yes/ 0 for no)> <baseline> <week1> <week2> <week3> <week4>… <week12>;

run;

**** Difelikefalin ***;*

*** Repeat the above process, replacing the seed numbers sequentially as follows:*

- 976031
- 864989
-

*** MMRM analysis for multiple imputed data;*

Please refer to the subsection 1. SAS code for MMRM in Appendix 4 and add "by _Imputation_;"

*** Summarized by the SAS MIANALYZE procedure;*

proc MIANALYZE data= <indatax>;

modeleffects <Estimate>;

stderr <StdErr>;

by <visit> <treatment code>;

ods output parameterestimates = <outdatax>;

run;

3. SAS code for Placebo MI – MMRM

*** Before the imputation, firstly create a variable "ref" to indicate the records with completed data in placebo treatment in dataset <indata>.*

For subjects with non-missing values from baseline to week 12 in placebo treatment, set variable "ref" =1; for all other records, set variable "ref" =0, which includes subjects with missing data in placebo treatment and subjects in difelikefalin treatment.;

****The first stage of imputation will create monotone missing data, the same output data from the first step of 2. SAS code for Multiple Imputation (MI) – MMRM, will be used.*

****After imputation of non-monotone missing data, the output datasets for each treatment group will be appended together and used in the following step to impute monotone missing data, with reference to the Placebo arm for imputations ("ref" = 1);*

proc mi data = <outdata1> nimpute=1 MINMAXITER=1000000 seed=328110 MAXIMUM=10 MINIMUM=0 out=<outdata2>;

by _Imputation_;

class ref;

monotone reg;mnar model (<week1> <week2> <week3> <week4> … <week12>/modelobs=(ref='1'));

var <use of prior anti-itch medication (1 for yes/ 0 for no)> <presence of specific medical conditions (1 for yes/ 0 for no)> <baseline> <week1> <week2> <week3> <week4> … <week12>;

run;

*** MMRM analysis for multiple imputed data;*

Please refer to 1. SAS code for MMRM in Appendix 4 and add "by _Imputation_;"

**** Summarized by the SAS MIANALYZE procedure;*

proc MIANALYZE data= <indatax>;

modeleffects <Estimate>;

stderr <StdErr>;

by <visit> <treatment code>;

ods output parameterestimates = <outdatax>;

run;

4. SAS code for – Logistic Regression Model

The logistic regression model will be implemented through PROC GENMOD in SAS.

**** Logistic regression model for multiple imputed data:*

ods output Diffs = Diffs

Lsmeans = Lsmeans

ConvergenceStatus = CS;

proc genmod data=<data> descending;

by _Imputation_ <visit>;

class <treatment code> <use of prior anti-itch medication (yes/no)> <presence of specific medical conditions (yes/no)>;

model <parameter> = <treatment code> <use of prior anti-itch medication (yes/no)> <presence of specific medical conditions (yes/no)> <baseline WI-NRS score>/dist=binomial link = logit;

lsmeans <treatment code>/ilink diff cl;

run;

ods output close;

In the above sample SAS code, for variable <parameter>, the subjects with ≥3-point or ≥4-point improvement is coded as "1", respectively, and the subjects not achieved ≥3-point or ≥4-point improvement is coded as "0".

**** Summarized "Estimate" and "StdErr" by the SAS MIANALYZE procedure, and then calculate the responder rate and 95% by the formulas below with the data in "<Estimates_lsm>";*

proc MIANALYZE data= Lsmeans;

modeleffects Estimate;

stderr StdErr;

by <visit> <treatment code>;

ods output parameterestimates = <Estimates_lsm> VarianceInfo = <VarianceInfo_lsm>;

run;

**** formulas;*

*The estimate of responder rate = 100*exp(estimate)/ (1+exp (estimate));*

*The lower limit of the 95% CI = 100*exp (LCLMean)/ (1+exp (LCLMean));*

*The upper limit of the 95% CI = 100*exp (UCLMean)/ (1+exp (UCLMean)).*

**** Summarized "Odds Ratio (95% CI)" by the SAS MIANALYZE procedure, and then calculate the Odds Ratio and 95% by the formulas below with the data in "<Estimates_diff>";*

proc MIANALYZE data=Diffs;

modeleffects Estimate;

stderr StdErr;

by <visit> <treatment code>;

ods output parameterestimates=<Estimates_diff> VarianceInfo=<VarianceInfo_diff>;

run;

**** formulas;*

The pooled Odds Ratio = exp(estimate);

The lower limit of the 95% CI = exp (LCLMean);

The upper limit of the 95% CI = exp (UCLMean).

5. SAS code for – Cochran-Mantel-Haenszel exact test

The Cochran-Mantel-Haenszel statistics will be implemented through PROC FREQ in SAS. And the following SAS code will be used:

ods output CMH = CMH

CommonOddsRatioCl = CommonOddsRatioCl

CommonOddsRatioTest = CommonOddsRatioTest;

proc freq data=<data>;

*table <use of prior anti-itch medication (yes/no)> * <presence of specific medical conditions (yes/no)> * <treatment code> * <parameter> / CMH;*

exact comor;

run;

ods output close;

In the above sample SAS code, for <parameter>, the subjects rate their itch condition as "Very much improved" or "Much Improved" are coded as "Yes" and the remaining with non-missing response are coded as "No", respectively.

SAS code for – Clopper-Pearson 95% CIs

The 2-sided exact Clopper-Pearson 95% CI of each treatment will be implemented through PROC FREQ in SAS as the following SAS code.

ods output Binomial = Binomial;

proc freq data=<data>;

by <treatment code>;

table <parameter> /nocum binomial (level ="Yes");

run;

ods output close;

In the above sample SAS code, for <parameter>, the subjects rate their itch condition as “Very much improved” or “Much Improved” are coded as “Yes” and the remaining with non-missing response are coded as “No”, respectively.