Statistical Analysis Plan

Title of Study:	A phase II clinical study of MR13A9 in previously treated hemodialysis patients with pruritus
Protocol No.:	MR13A9-4
Version:	1.0
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1. Clinical Study Protocol

This statistical analysis plan was created according to the clinical study protocol (Version, 02.00.000; date of creation/amendment: November 29, 2018).

2. Changes from the Clinical Study Protocol

1) Changes in the statistical analysis plan version 1.0

(1) For NRS scores, responder rate in the mean NRS score was added.
Reason: It was added to perform the evaluation from the same viewpoint as the US phase II study (CLIN2101).

(2) For the changes from baseline in itch score based on the Shiratori's severity criteria, Skindex-16 and 5-D Itch Scale, an analysis using a mixed effects model for repeated measures (MMRM) was added as in "10.1.1.1.1 Primary analysis."
Reason: It was added to perform the evaluation from the same viewpoint as the US phase II study (CLIN2101).

(3) The score terms of Skindex-16 was changed.
Reason: It was changed to use an appropriate terms.

(4) For adverse events and adverse drug reactions, tabulation of adverse events of special interest was added.
Reason: It was added to carefully evaluate the effects on the central nervous system.

3. General Matters

All statistical tests will be performed using a two-sided significance level of 5%; however, a two-sided significance level of 15% will be used for the analysis of between-group imbalance. Summary statistics will be presented as the number of subjects, mean, standard deviation, minimum, median, maximum, and quartile. Unless otherwise specified, data will be tabulated by group and by time point. Week 0 will be the baseline.
SAS System Release 9.4 for Windows (SAS Institute Inc.) will be used to conduct the analysis.

4. Analysis Sets

The analysis sets are defined as follows. When the full analysis set (FAS) and the per protocol set (PPS) are used as analysis sets, analyses will be performed based on the treatment group to which each subject has been allocated. When the safety set (SS) and the pharmacokinetic analysis set (PKS) are used as analysis sets, analyses will be performed based on the treatment group in which each subject has been actually treated.

- FAS: Population of subjects, excluding the following subjects: subjects with GCP violations, untreated subjects, discontinued subjects before entry to the treatment period, some of the ineligible subjects, and subjects with no available mean NRS score at baseline (Week 0)
- PPS: Population of subjects, excluding the following subjects from the FAS: ineligible subjects, discontinued subjects, deviators, and subjects with broken emergency key codes, as the subjects to be excluded from the PPS

- SS: Population of subjects, excluding the following subjects: subjects with GCP violations, untreated subjects, and discontinued subjects before entry to the treatment period
- PKS: Population of subjects, excluding the following subjects from the SS: subjects with no available plasma drug concentration data

Correspondence of the analysis items and the analysis sets is shown in Table 4-1.

Table 4-1 Analysis Items and Analysis Sets

Endpoints	Analysis items	Analysis sets
Demographic and other baseline characteristics	Subject demographics	FAS, PPS, SS, PKS
	Other	SS
Treatment compliance	All items	FAS, SS
Efficacy	Primary variable (primary analysis)	FAS (primary analysis set), PPS
	Other	FAS
Pharmacokinetics	All items	PKS
Safety	All items	SS

5. Analysis Groups

- MR13A9 0.25 μg/kg group: Subjects allocated to or treated with MR13A9 0.25 μg/kg
- MR13A9 0.5 μg/kg group: Subjects allocated to or treated with MR13A9 0.5 μg/kg
- MR13A9 1.0 μg/kg group: Subjects allocated to or treated with MR13A9 1.0 μg/kg
- Placebo group: Subjects allocated to or treated with placebo

6. Statistical/Analytical Issues

6.1 Adjustments for Covariates

The change from baseline in the mean NRS score at Week 8 of the treatment period, the primary variable, will be analyzed using the baseline mean NRS score and dynamic allocation factors, including the presence of prior treatment with nalfurafine hydrochloride, and the presence of specific signs or symptoms to be confirmed in the screening period as covariates. The details are shown in "10.1.1.1 Analysis of the primary variable." If an imbalance is observed in the subject demographic in the FAS, the primary analysis set for efficacy, a supplementary analysis will be performed with additional items showing the imbalance as the covariates in the primary analysis.
For the changes from baseline in the itch score based on the Shiratori's severity criteria, changes from baseline in Skindex-16, and changes from baseline in 5-D Itch Scale, an analysis will be performed using baseline as a covariate for each item. Details are shown in "10.2.1.1 Changes from the baseline in the itch score based on the Shiratori's severity criteria," "10.2.2.1 Changes from baseline in Skindex-16," and "10.2.3.1 Changes from baseline in 5-D itch scale," respectively.

6.2 Handling of Dropouts or Missing Data

When there is a lack in the data used for analysis, all items other than the following items will be handled as missing values, and no imputation by statistical methods will be performed.
Sensitivity analyses of the primary variable will use multiple imputation. The details are shown in "10.1.1.1.2 Sensitivity analysis."
If the number of days of observation during the evaluation period is less than 4 days as of the time of calculation of the mean NRS score and the mean itch score based on the Shiratori's severity criteria at each time point, the score at that time point will be handled as missing.
If the overall score or the subscores (symptoms score, emotions score, and functioning score) of the Skindex-16 or the responses to the questions used for calculation of the total score of 5-D Itch Scale are missing, the score will be handled as missing.
Any plasma drug concentration below the lower limit of quantification (BLQ) will be treated as 0.
Any BLQ values observed in laboratory test values will be handled as the values of the quantification limit.
In the calculation of geometric mean and geometric CV, values of 0 before log-transformation will be handled as missing values.

6.3 Interim Analyses and Data Monitoring

Not performed.

6.4 Multicenter Study

Since the number of subjects per site is not large, analysis by site will not be performed.

6.5 Multiplicity

6.5.1 Multiplicity at multiple evaluation time points

Since Week 8 of the treatment period is defined as the primary evaluation time point and evaluations at other time points are handled as references, multiplicity at multiple evaluation time points is not adjusted.

6.5.2 Multiplicity among multiple items

Since the change from baseline in the mean NRS score at Week 8 of the treatment period is handled as the primary variable, and other items are handled as references, multiplicity among multiple items will not be adjusted.

6.5.3 Multiplicity among multiple groups

For the primary variable, multiplicity among multiple groups will not be adjusted because the dose-response relationship between the placebo group and the MR13A9 0.25, 0.5, and 1.0 μg/kg groups will be examined using contrasts.
Since other items are handled as references, multiplicity among multiple groups will not be adjusted.

6.5.4 Multiplicity of multiple analysis sets

For efficacy, the FAS will be used as the primary analysis set, and the PPS will be used for the supplemental analysis to examine the robustness of the results, so multiplicity among multiple analysis sets will not be adjusted. It is not applicable for safety because only the SS is used as the analysis set. It is not applicable for pharmacokinetics because only the PKS is used as the analysis set.

6.6 Use of "Two Different Analysis Sets for Efficacy Evaluation" of Subjects

The primary efficacy analysis set will be the FAS. On the other hand, the analysis will also be performed in the PPS as a supplemental analysis to examine the robustness of the results. The definitions of FAS and PPS are detailed in "4 Analysis Sets."

6.7 Active-controlled Studies Intended to Show Non-inferiority

Not applicable.

6.8 Examination of Subgroups

As the subgroup analyses of efficacy endpoints, the matters shown in "10.3 Efficacy Subgroups" will be performed. As the subgroup analyses of safety endpoints, the matters shown in "12.5 Safety Subgroups" will be performed.

7. Disposition of Subjects

The subjects who entered the treatment period will be analyzed.

7.1 Analysis Sets

The numbers and percentages of subjects will be presented for the analysis sets shown in Table 7.1-1, and between-group imbalance will be examined by Fisher's exact test.

Table 7.1-1 Category

Analysis Sets	Category
FAS	Included, excluded
PPS	Included, excluded
SS	Included, excluded
PKS	Included, excluded

7.2 Presence or Absence and Reasons of Discontinuation

The numbers and percentages of subjects for presence/absence of discontinuation during the treatment period will be presented, and between-group imbalance will be examined by Fisher's exact test.
For the reasons of discontinuation in the treatment period, the number and percentage of subjects will be presented for each category shown in Table 7.2-1.

Table 7.2-1 Category

Category	Reason for discontinuation
Adverse event	When the reason for discontinuation during the treatment period entered in the case report form falls under the category of "adverse event"
Lack of efficacy	When the reason for discontinuation during the treatment period entered in the case report form falls under the category of "lack of efficacy"
Withdrawal by subject	When the reason for discontinuation during the treatment period entered in the case report form falls under the category of "Withdrawal by subject "
Protocol deviation	When the reason for discontinuation during the treatment period entered in the case report form falls under the category of "protocol deviation"
Others	When the reason for discontinuation during the treatment period does not fall under the categories of “adverse events,” “lack of efficacy,” “withdrawal by subject,” or “protocol deviation.”

8. Demographic and Other Baseline Characteristics

8.1 Subject Demographics

The numbers and percentages of subjects are presented overall and by group for the variables shown in Table 8.1-1 and Table 8.1-2 and summary statistics are presented for the variables shown in Table 8.1-3. However, only the number of subjects is shown for the primary disease of dialysis. If there are data at more than one time point before the start of the treatment period, the data at Week 0 will be used for the evaluation of subject demographic.
The between-group imbalance will be examined by tests for the prior treatment with nalfurafine hydrochloride, specific signs or symptoms to be confirmed in the screening period, dry weight at the start of the screening period (ordinal scale variable), and mean NRS score. Depending on the characteristics of the data, Fisher's exact test will be used for nominal scale variables, Kruskal-Wallis test for ordinal scale variables, and one-way analysis of variance for continuous variables.

Table 8.1-1 Nominal Scale Variables

Item	Category
Sex	Male, female
Primary disease of dialysis	Diabetic nephropathy, glomerulonephritis chronic, nephrosclerosis, polycystic kidney, pyelonephritis chronic, other, unspecified
Type of dialysis	HD, off-line HDF, on-line HDF, I-HDF
Vascular access	Arteriovenous fistula, arteriovenous graft, external shunt, subcutaneously fixed superficial artery, percutaneous venous catheter, direct arterial puncture, other
Remaining renal function	No, Yes
Prior treatment with nalfurafine hydrochloride	No, Yes
Specific signs or symptoms to be confirmed in the screening period[a)]	No, Yes

a) Specific signs or symptoms: dizziness, syncope, palpitations, tachycardia, fall, seizure, gait disturbance, mental status changes, somnolence, mood changes

Table 8.1-2 Ordinal Scale Variables

Item	Category
Age	< 65 years, ≥ 65 years
Dry weight at the start of the screening period	< 45 kg, ≥ 45 and < 65 kg, ≥ 65 and < 85 kg, ≥ 85 kg

Table 8.1-3 Continuous Variables

Item
Age, dry weight at the start of the screening period, hemodialysis history, single-pool Kt/V, urea reduction ratio, disease duration of itch, mean NRS score, itch score based on the Shiratori's severity criteria (higher of daytime or night-time), Skindex-16 (overall score), 5-D Itch Scale (total score)

8.2 Complication

The numbers and percentages of subjects are presented for all complications and by primary SOC and PT.

8.3 Concomitant Medications for Target Disease (Itching)

For concomitant medications used for the treatment of the target disease (itching) from the start of the study treatment to the end of the treatment period, the numbers and percentages of subjects will be presented by generic name and route of administration.

8.4 Concomitant Medications for Complications

For the concomitant medications used for complications from the start of the study treatment to the end of the treatment period, the numbers and percentages of subjects will be presented by generic name and route of administration.

9. Treatment compliance

9.1 Number of Doses

For the number of doses of the study drug, the numbers and percentages of subjects who fall under the following categories will be presented.

Category: $1 \leq \leq 3$, $4 \leq \leq 6$, $7 \leq \leq 9$, $10 \leq \leq 12$, $13 \leq \leq 15$, $16 \leq \leq 18$, $19 \leq \leq 21$, $22 \leq \leq 24$, $25 \leq$ (unit: times)

9.2 Treatment Compliance

Summary statistics will be presented.

9.3 Treatment Duration

Summary statistics will be presented.

9.4 Average Administration Liquid Volume

The average administration liquid volume will be obtained by dividing the total administration liquid volume of the study drug in the treatment period by the number of doses. Summary statistics will be presented.

9.5 Change Status of Administration Liquid Volume

For changes from the initial administration liquid volume throughout the treatment period, the

numbers and percentages of subjects who fall under the following categories will be presented.

Category:

- No change: Subjects who received only the initial administration liquid volume throughout the treatment period
- Dose increase: Subjects who received an administration liquid volume larger than the initial administration liquid volume (excluding the cases with a dose increase and decrease)
- Dose decrease: Subjects who received an administration liquid volume smaller than the initial administration liquid volume (excluding the cases with a dose increase and decrease)
- Dose increase and decrease: Subjects who received administration liquid volumes larger and smaller than the initial administration liquid volume

9.6 Average Dose per Dry Weight

The total dose of the study drug per dry weight during the treatment period is divided by the number of doses to obtain the average dose per dry weight.
Summary statistics will be presented.

10. Efficacy

10.1 Primary Endpoint

The primary endpoint is the NRS score. The assessment time points and their evaluated time windows in the screening and treatment periods, and follow-up period are shown in Table 10.1-1 and Table 10.1-2, respectively.

Table 10.1-1 Assessment Time Points and Evaluated Time Windows in the Screening and Treatment Periods

Time point	Evaluated time window[a)]
Week −1	From Day −13 to Day −7
Week 0 (baseline)	From Day −6 to Day 1
Week 1	From Day 2 to Day 8
Week 2	From Day 9 to Day 15
Week 3	From Day 16 to Day 22
Week 4	From Day 23 to Day 29
Week 5	From Day 30 to Day 36
Week 6	From Day 37 to Day 43
Week 7	From Day 44 to Day 50
Week 8	From Day 51 to Day 57

a) The start date of the treatment period will be regarded as Day 1 and the previous day of the start date of the treatment period will be regarded as Day −1.

Table 10.1-2 Assessment Time Points and Evaluated Time Windows in the Follow-up Period

Time point	Evaluated time window[a)]
Follow-up Week 1	From Day 1 to Day 7
Follow-up Week 2	From Day 8 to Day 14

a) The start date of the follow-up period (the date of treatment period completion or the next day of the date of discontinuation) will be regarded as Day 1.

The mean NRS score at each time point will be calculated as follows.

> Mean NRS score at each time point = Sum of the NRS score observed during the evaluated time window ÷ Number of days when NRS score was observed during the evaluated time window

The change from baseline in the mean NRS score at each time point will be calculated as follows:

> Change from baseline in the mean NRS score at each time point = Mean NRS score at each time point − Mean NRS score at baseline

10.1.1 Primary variable

Change from baseline in the mean NRS score at Week 8 of the treatment period

10.1.1.1 Analysis of the primary variable

10.1.1.1.1 Primary analysis

The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with the change from baseline in the mean NRS score at each time point as an objective variable; treatment group, time point, and treatment group-by-time point interaction as fixed effects; baseline mean NRS score and dynamic allocation factors, including the presence of prior treatment with nalfurafine hydrochloride, and the presence of specific signs or symptoms to be confirmed in the screening period, as covariates; and subject as a random effect.
The analysis will include all available data obtained at each time point between Week 1 and Week 8 of the treatment period. Estimation will be performed using a restricted maximum likelihood method. An unstructured covariance structure will be used to estimate error variance. If the unstructured covariance structure fails to provide convergence, the structure that minimizes Akaike's Information Criterion (AIC), among the Toeplitz, first-order autoregressive, and compound symmetry structures will be used. The degree of freedom will be adjusted with the Kenward-Roger method.
For the primary variable and the change from baseline in the mean NRS score at Week 2 of the treatment period, contrasts will be used to determine the dose-response relationship for the placebo group and the MR13A9 0.25, 0.5, and 1.0 μg/kg groups. Contrast patterns (placebo, 0.25, 0.5, 1.0 μg/kg) to be used will include (3, 1, −1, −3), (2, 2, −1, −3), (1, 1, 1, −3), (1, 1, −1, −1), (3, −1, −1, −1), and (3, 1, −2, −2).
The number of subjects, adjusted mean of the change, standard error, and two-sided 95% confidence interval in each group at each time point will be presented, and the adjusted mean and standard error will be presented in graphs. The adjusted mean between-group difference in the change at each time point for the placebo group and the MR13A9 0.25, 0.5, and 1.0 μg/kg groups and its two-sided 95% confidence interval as well as the p-value will be

presented. P-values will be presented for each contrast pattern used to examine the dose-response relationship.

Assessment time points: Weeks 1, 2, 3, 4, 5, 6, 7, and 8

10.1.1.1.2 Sensitivity analysis

The sensitivity analyses shown below will be performed to determine the robustness of the analysis results. In the individual sensitivity analyses, as with the primary analysis, contrasts will be used to determine dose-response relationships and estimate treatment effects. However, this is not presented in graphs.
Multiple imputation (MI) will be performed 100 times.

1) MI - MMRM

Multiple imputed data will be generated in the MI procedures shown below. Each imputation data will be analyzed using the same MMRM model as that for the primary analysis, and the results of the analyses will be combined. Imputation will be performed for all available data obtained at each time point between Week 0 and Week 8 of the treatment period.

(1) Non-monotone missing data will be imputed with a Markov Chain Monte Carlo (MCMC) method.

(2) Monotone missing data will be imputed with an imputation formula generated using a regression model developed based on the data from all the groups.

2) Placebo MI - MMRM

Multiple imputed data will be generated in the MI procedures shown below. Each imputation data will be analyzed using the same MMRM model as that for the primary analysis, and the results of the analyses will be combined. Imputation will be performed for all available data obtained at each time point between Week 0 and Week 8 of the treatment period.

(1) Non-monotone missing data will be imputed with an MCMC method.

(2) Monotone missing data will be imputed with an imputation formula generated using a regression model developed based on the data from the placebo group.

10.1.2 Other assessment variables

10.1.2.1 Change from baseline in the mean NRS score

Summary statistics will be presented. A one-sample t-test will be used for comparisons within each group. A two-sample t-test will be used for comparisons between the placebo group and each of the MR13A9 0.25, 0.5, and 1.0 μg/kg groups.

Assessment time points: Weeks 1, 2, 3, 4, 5, 6, 7, and 8, Follow-up Weeks 1 and 2

10.1.2.2 Mean NRS score

Summary statistics will be presented. Means and standard deviations will be presented graphically.

Assessment time points: Weeks −1, 0, 1, 2, 3, 4, 5, 6, 7, and 8, Follow-up Weeks 1 and 2

10.1.2.3 Responder rate in mean NRS score

The numbers and percentages of responders shown below will be presented. Fisher's exact test will be used for comparisons between the placebo group and each of the MR13A9 0.25, 0.5, and 1.0 μg/kg groups. The percentages of responders will be presented graphically.

3 points responder:	The change in the mean NRS score from baseline is −3 or less.
4 points responder:	The change in the mean NRS score from baseline is −4 or less.
Assessment time points:	Weeks 1, 2, 3, 4, 5, 6, 7, and 8, Follow-up Weeks 1 and 2

10.2 Secondary Endpoints

10.2.1 Itch score based on the Shiratori's severity criteria

Analysis items are shown below.

Itch score based on the Shiratori's severity criteria: Higher of daytime or night-time; daytime and night-time

The mean itch score and the change from baseline at each time point will be calculated using the same calculation formula as that for the mean NRS score and change from baseline shown in "10.1 Primary Endpoint."

10.2.1.1 Changes from the baseline in the itch score based on the Shiratori's severity criteria

The same analysis as "10.1.1.1.1 Primary analysis" will be performed. However, the baseline of each item will be used as a covariate in the model. Examination of the dose-response relationship using contrasts will not be conducted. The same analysis as "10.1.2.1 Change from baseline in the mean NRS score" will be performed.

Assessment time points: (analysis using a model) Weeks 1, 2, 3, 4, 5, 6, 7, and 8
(Others) Weeks 1, 2, 3, 4, 5, 6, 7, and 8, Follow-up Weeks 1 and 2

10.2.1.2 Itch score based on the Shiratori's severity criteria

The same analysis as "10.1.2.2 Mean NRS score" will be performed.

Assessment time points: Weeks −1, 0, 1, 2, 3, 4, 5, 6, 7, and 8, Follow-up Weeks 1 and 2

10.2.2 Skindex-16

Subscores will be the symptoms score, emotions score, and functioning score.
Analysis items are shown below.

Skindex-16: Overall score, subscores (symptoms, emotions, and functioning)

10.2.2.1 Changes from baseline in Skindex-16

The same analysis as "10.1.1.1.1 Primary analysis" will be performed. However, the baseline

of each item will be used as a covariate in the model. Examination of the dose-response relationship using contrasts will not be conducted. The same analysis as "10.1.2.1 Change from baseline in the mean NRS score" will be performed.

Assessment time points: Weeks 4 and 8

10.2.2.2 Skindex-16

The same analysis as "10.1.2.2 Mean NRS score" will be performed.

Assessment time points: Weeks 0, 4, and 8

10.2.3 5-D Itch Scale

Analysis items are shown below.

5-D Itch Scale: Total score

10.2.3.1 Changes from baseline in 5-D itch scale

The same analysis as "10.1.1.1.1 Primary analysis" will be performed. However, baseline of the total score will be used as a covariate in the model. Examination of the dose-response relationship using contrasts will not be conducted. The same analysis as "10.1.2.1 Change from baseline in the mean NRS score" will be performed.

Assessment time points: Weeks 4 and 8

10.2.3.2 5-D Itch Scale

The same analysis as "10.1.2.2 Mean NRS score" will be performed.

Assessment time points: Weeks 0, 4, and 8

10.2.4 Patient Global Impression of Change (PGIC)

For measurements, the number and percentage of subjects will be presented. A two-sample Wilcoxon test will be used for comparisons between the placebo group and each of the MR13A9 0.25, 0.5, and 1.0 μg/kg groups. The percentages for measurements will be presented graphically.

Assessment time points: At final assessment in the treatment period

10.3 Efficacy Subgroups

Among "10.1.1.1 Analysis of the primary variable," the same analysis as "10.1.1.1.1 Primary analysis" will be performed for each subgroup shown in Table 10.3-1. However, the subgroup variables will be excluded from the model covariates. Assessment of the dose-response relationship using contrasts will not be conducted.

Table 10.3-1 Subgroups

Item	Class
Prior treatment with nalfurafine hydrochloride	No, Yes
Specific signs or symptoms to be confirmed in the screening period	No, Yes

11. Pharmacokinetics

11.1 Evaluation of Plasma Drug Concentration

Analysis groups other than the placebo group will be used. Analysis items are shown below.

Plasma drug concentration: Plasma MR13A9 (unchanged drug) concentration

11.1.1 Plasma drug concentration

Summary statistics, geometric mean, and geometric CV will be presented. Geometric means and individual values will be illustrated by dose group.

Assessment time points: Week 1 (before the first dialysis of the week, 5 minutes after administration, before the second dialysis of the week),
Week 2 (before the first dialysis of the week),
Week 4 (before the first dialysis of the week, 5 minutes after administration, and before the second dialysis of the week),
Week 7 (before the first dialysis of the week, 5 minutes after administration, 1 hour after administration, and before the second dialysis of the week),
Week 8 (before the first dialysis of the week)

11.1.2 Plasma drug concentration profile

For Week 1 (before the first dialysis of the week, 5 minutes after administration, and before the second dialysis of the week), Week 4 (before the first dialysis of the week, 5 minutes after administration, and before the second dialysis of the week) and Week 7 (before the first dialysis of the week, 5 minutes after administration, and before the second dialysis of the week), the mean values at each time point will be graphically presented by superimposing the dose group.
For Week 1 (before the first dialysis of the week, before the second dialysis of the week), Week 2 (before the first dialysis of the week), Week 4 (before the first dialysis of the week, before the second dialysis of the week), Week 7 (before the first dialysis of the week, before the second dialysis of the week) and Week 8 (before the first dialysis of the week), the mean and standard deviation at each time point will be graphically presented by superimposing the dose group.
For the data at 5 minutes after administration at Weeks 1, 4, and 7, the mean and standard deviation at each time point will be graphically presented by superimposing the dose group.

11.1.3 Plasma drug concentration (Week 7)

For subjects with data obtained at least 1 hour after administration at Week 7, the time course of the measured value in each subject relative to the time (unit: hour) after administration of the study drug on dialysis at Week 7 (before the first dialysis of the week, 5 minutes after administration, at least 1 hour after administration, and before the second dialysis of the week) is presented.

11.1.4 Plasma drug concentration (dry weight category)

Summary statistics, geometric means, and geometric CVs are presented for the following dry weight categories. Geometric means and individual values will be presented graphically for each dose group for the following dry weight categories. The dry weight category is based on the dry weight at the assessment time points.

Dry weight category: < 45 kg, ≥ 45 and < 65 kg, ≥ 65 and < 85 kg, ≥ 85 kg

Assessment time points: Week 1 (before the first dialysis of the week, 5 minutes after administration),
Week 4 (before the first dialysis of the week, 5 minutes after administration),
Week 7 (before the first dialysis of the week, 5 minutes after administration),

11.1.5 Time elapsed after administration (Week 7, at least 1 hour after administration)

The time elapsed from the study drug administration to blood sampling for plasma drug concentration at the time point of assessment is regarded as the time elapsed after the last administration (unit: hour).
Summary statistics will be presented only for data obtained at least 1 hour after administration at Week 7.

12. Safety

12.1 Adverse Events and Adverse Drug Reactions

Unless otherwise specified, the following events will be tabulated.

- Events occurring between the start of study treatment and the end of the follow-up period
- Events occurring between the start of study treatment and the end of the treatment period
- Adverse events of special interest occurring between the start of study treatment and the end of the follow-up period
- Adverse events of special interest occurring between the start of study treatment and the end of the treatment period

12.1.1 Incidence of adverse events and adverse drug reactions

The number of events, the number of subjects experiencing events, the incidence of events and its two-sided 95% confidence interval will be presented. Fisher's exact test will be used for comparisons between the placebo group and each of the MR13A9 0.25, 0.5, and 1.0 μg/kg groups. The difference in the incidence between the placebo group and the MR13A9 0.25, 0.5, and 1.0 μg/kg groups and its two-sided 95% confidence interval will be presented.

12.1.2 Incidences of adverse events and adverse drug reactions (serious adverse events, adverse events leading to discontinuation of treatment period, and adverse events of special interest)

For adverse events occurring between the start of study treatment to the end of the follow-up

period, and adverse events between the start of treatment with the study drug to the end of the treatment period, the number of events, the number of subjects experiencing events, and the incidence of all events, adverse events leading to death, serious adverse events excluding death, events leading to interruption, events leading to discontinuation of the treatment period, and adverse events of special interest will be presented.

12.1.3 Occurrence of adverse events and adverse drug reactions

The number of subjects experiencing events and the incidence of events will be presented for all events and by primary SOC and PT.

12.1.4 Occurrence of adverse events and adverse drug reactions (by severity)

The numbers of events by severity will be presented for all events and by primary SOC and PT.

12.1.5 Details of adverse events of special interest

For adverse events of special interest occurring between the start of the study treatment to the end of the follow-up period, the number of events, the number of subjects experiencing events, and incidence of adverse events and adverse drug reactions will be presented, and the number of events for each category in Table 12.1.5-1 will be presented.

Table 12.1.5-1 Analysis Items

Item	Category
Severity	Mild, moderate, severe
Action taken with study treatment	Drug withdrawn, drug interrupted, dose not changed, unknown, not applicable
Outcome	Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, and unknown
The period of recovered/resolved	Treatment period, follow-up period or later

12.2 Laboratory Tests

Analysis items are shown below.

Laboratory tests: Red blood cell count, hemoglobin, hematocrit, white blood cell count, differential white blood cell count (neutrophil, eosinophil, basophil, monocyte, lymphocyte), platelet count, AST, ALT, γ-GTP, CRP, LDH, ALP, total protein, albumin, glycoalbumin, glucose, total cholesterol, total bilirubin, direct bilirubin, creatinine, BUN (before dialysis), Na, K, Cl, Ca, P, serum iron, UIBC, TIBC, TSAT, ferritin, testosterone, free testosterone, prolactin, TSH, FT3, FT4, intact-PTH, antidiuretic hormone

12.2.1 Laboratory tests

Summary statistics will be presented.

Assessment time points: Weeks −2, 0, 1, 2, 4, and 8, end of the treatment period, and Follow-up Week 2

12.2.2 Shift table of laboratory data

The numbers and percentages of subjects with low, normal, or high values before and after administration will be presented.

Assessment time points: Week 0 and end of the treatment period

12.2.3 Scatterplots of laboratory tests

Scatterplots of measurements before and after treatment will be presented.

Assessment time points: Week 0 and end of the treatment period

12.3 Vital Signs and Body Weight

Analysis items are shown below.

Vital signs: Systolic blood pressure, diastolic blood pressure, pulse rate, and body temperature
Body weight (before dialysis)

12.3.1 Vital Signs and Body Weight

Summary statistics will be presented.

Assessment time points: Shown in Table 12.3.1-1.

Table 12.3.1-1 Assessment Time Points

Item	Assessment Time Points
Vital signs	Weeks −2, 0, 1, 2, 4, and 8, end of the treatment period, and Follow-up Week 2
Body weight	Weeks −2, 0, and 8, and end of the treatment period

12.3.2 Scatter plots of vital signs and body weight

Scatterplots of measurements before and after treatment will be presented.

Assessment time points: Week 0 and end of the treatment period

12.4 Dependency Assessment

12.4.1 Evaluation of dependency based on judgment by dependency assessment members

The numbers and percentages of subjects will be presented by category in Table 12.4.1-1. However, only subjects with dependence will be included in the tabulation of severity.

Table 12.4.1-1 Category

Item	Category
Dependency	Negative, positive, not evaluable
Severity	Mild, moderate, severe

12.5 Safety Subgroups

The same analysis as "12.1.1 Incidence of adverse events and adverse drug reactions" will be performed for each subgroup shown in Table 12.5-1.

Table 12.5-1 Subgroups

Item	Category
Sex	Male, female
Age	< 65 years, ≥ 65 years
Prior treatment with nalfurafine hydrochloride	No, Yes
Specific signs or symptoms to be confirmed in the screening period	No, Yes

13. Tabulated Lists

The following lists will be prepared for subjects who entered the treatment period. However, the lists will not be prepared if there is no applicable event.

- Deaths
- Serious adverse events excluding deaths
- Adverse events leading to interruption
- Adverse events leading to discontinuation during the treatment period
- Adverse events of special interest
- Abnormal laboratory values by subject

14. History of Preparation

Prepared on January 20, 2020 Version: 1.0

CERTIFICATE OF TRANSLATION

This document is the translated version of the source document below written in Japanese.
It is hereby certified that this document is a true and accurate translation of the source document from Japanese into English.

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