CLINICAL STUDY PROTOCOL

Development Code : MR13A9
Study Type : Phase II Clinical Study
Study Population : Previously Treated Hemodialysis Patients with Pruritus

Study Objectives:

To determine the dose-response relationship for the efficacy, safety, and pharmacokinetics of MR13A9 0.25, 0.5, or 1.0 μg/kg administered to previously treated hemodialysis patients with pruritus for 8 weeks in a placebo-controlled, double-blind design.

Title of Study:

A phase II clinical study of MR13A9 in previously treated hemodialysis patients with pruritus

Development Phase:

Phase II

Protocol No.:

MR13A9-4

Version:

02.00.000

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Sponsor:

Kissei Pharmaceutical Co., Ltd.

[redacted]

Protocol Synopsis

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(Protocol No.: MR13A9-4)

Development Phase:
Phase II

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1. Efficacy endpoints
1) Primary endpoint
• Itch NRS score (The primary variable is change from baseline in the mean NRS score at Week 8 of the treatment period)
2) Secondary endpoints
• Itch score based on the Shiratori's severity criteria
• Skindex-16 score
• 5-D itch scale score
• Patient Global Impression of Change (PGIC)
2. Safety endpoints
• Occurrence of adverse events
• Occurrence of adverse drug reactions
• Occurrence of adverse events of special interest
• Laboratory tests (hematology, blood biochemistry, endocrinology)
• Vital signs (blood pressure, pulse rate, body temperature)
• Body weight
• 12-lead ECG
• Dependency assessment
3. Pharmacokinetic endpoint
• Plasma concentration of MR13A9 (unchanged drug)

Study Population:
This study will enroll previously treated hemodialysis patients with pruritus who meet all of the inclusion criteria and none of the exclusion criteria below.

1. Inclusion criteria
1) Patients aged 20 years or older (at the time of signing informed consent)
2) Japanese patients providing written informed consent for study participation in person (Their first- and second-degree relatives must be all Japanese)
3) Patients with chronic renal failure on periodic hemodialysis (HD, off-line HDF, on-line HDF, or I-HDF) 3 times weekly for ≥ 12 weeks prior to the informed consent procedure who can continue hemodialysis without changing its frequency or method (excluding temporary changes with no changes in treatment strategies) during the study
4) Patients whose pruritus treatment for 1 year prior to the informed consent procedure meets either (1) or (2) below:
   (1) Drug therapy with nalfurafine hydrochloride for ≥ 2 consecutive weeks
   (2) Inadequate response to both drug therapies a) and b) below:
      a) Systemic (e.g., oral, injection) therapy with antihistamines or antiallergics contained in prescription drugs indicated for the treatment of itching for ≥ 2 consecutive weeks
      b) Local (topical) therapy with prescription drugs indicated for the treatment of itching or moisturizers prescribed by physicians
5) Patients not receiving nalfurafine hydrochloride for ≥ 2 weeks prior to the start of the screening period
6) Patients whose pruritus has been treated with 1 or more drugs listed below since prior to the start of the screening period:
   • Drugs indicated for the treatment of itching (prescription/nonprescription) (excluding nalfurafine hydrochloride)
   • Moisturizing drugs (prescription/nonprescription)
   • Products formulated with either of the above
7) Patients whose NRS score in the 7 days prior to the start of the treatment period (including the score recorded on the day at Week 0) meets both of the below:
   • NRS scores have been recorded for ≥ 5 days.
   • The mean value of the recorded scores exceeds 4.
8) Patients whose itch score based on the Shiratori's severity criteria in the 7 days prior to the start of the treatment period (including the score recorded on the day at Week 0) meets both of the below:
   • Itch scores during the day and the night have been recorded for ≥ 5 days.
   • The larger itch score either during the day or the night is "3: Moderate itching" or greater for ≥ 2 days.
9) Patients who can record the symptom diary, as instructed by the principal investigator, subinvestigator, or clinical research coordinator

2. Exclusion criteria

1) Patients with itching caused by conditions other than chronic renal failure or complications of chronic renal failure, which could affect the efficacy evaluation in the opinion of the principal investigator or subinvestigator (e.g., atopic dermatitis, chronic urticaria)
2) Patients with concurrent hepatic cirrhosis
3) Patients who received phototherapy to treat itching within 4 weeks prior to the start of the screening period
4) Patients who previously received any study drug (including placebo) in a clinical study of MR13A9
5) Patients with any concurrent or previous disease that could affect the evaluations in this study in the opinion of the principal investigator or subinvestigator
6) Patients with any adverse drug reaction to nalfurafine hydrochloride in the past who are ineligible for study participation in the opinion of the principal investigator or subinvestigator
7) Patients with drug hypersensitivity to opioids
8) Patients whose laboratory data at the start of the screening period meets any of criteria (1) to (3):
   (1) ALT > 2.5 times the upper limit of normal
   (2) AST > 2.5 times the upper limit of normal
   (3) Total bilirubin > 2 times the upper limit of normal
9) Patients whose dry weight is < 24 kg at the start of the screening period
10) Patients with congestive heart failure (NYHA functional class IV) (Appendix 1)
11) Patients with concurrent malignancy or a history of malignancy within 5 years prior to the informed consent procedure
12) Patients with concurrent or previous drug abuse (defined as illicit drug use)
13) Patients with concurrent or previous alcoholism
14) Patients with a history of severe drug hypersensitivity
15) Patients with a mental disorder (i.e., depression, schizophrenia, or dementia) that could affect the evaluation of the investigational product
16) Female patients who are pregnant, breastfeeding, intending to become pregnant between the informed consent procedure and the end of the follow-up period, or unwilling to use appropriate methods to prevent conception
17) Male patients who are unwilling to use appropriate methods to prevent conception between the start of study treatment and 12 weeks after the day of the final dose
18) Patients who received treatment with any study drug or medical device in a clinical study (including clinical studies of medical devices) within 12 weeks prior to the informed consent procedure, or who are planning to participate in another clinical study before the end of the follow-up period of this study
19) Patients scheduled to be hospitalized to receive any medical intervention between the informed consent procedure and the end of the follow-up period
20) Patients withdrawn from the study in the screening period because they are found to not meet either inclusion criteria 7) or 8) after participation in the study
21) Patients withdrawn from the study in the screening period after re-registration
22) Other patients ineligible for study participation in the opinion of the principal investigator or subinvestigator

Study Design:

A placebo-controlled, multicenter, randomized, double-blind, parallel-group study

Study Drugs:

1. Test drug

• MR13A9 0.025 mg/mL (injection):
Each vial contains 1.3 mL of MR13A9 dissolved in 0.04 mol/L isotonic acetate buffer (pH 4.5) at a concentration of 0.025 mg/mL

• MR13A9 0.05 mg/mL (injection):
Each vial contains 1.3 mL of MR13A9 dissolved in 0.04 mol/L isotonic acetate buffer (pH 4.5) at a concentration of 0.05 mg/mL

• MR13A9 0.1 mg/mL (injection):
Each vial contains 1.3 mL of MR13A9 dissolved in 0.04 mol/L isotonic acetate buffer (pH 4.5) at a concentration of 0.1 mg/mL

2. Control drug

• MR13A9 placebo (injection):
Each vial contains 1.3 mL of 0.04 mol/L isotonic acetate buffer (pH 4.5)
The MR13A9 placebo is indistinguishable from MR13A9 0.025, 0.05, or 0.1 mg/mL.

Dose and Dosing Method:

1. Screening period

A 2-week period before entry into the treatment period is defined as the screening period, during which subjects will receive no study drug. Subjects will continuously use any restricted concomitant medications (e.g., anti-itch drugs) used at the start of the screening period.

2. Treatment period

In addition to the use of restricted concomitant medications (e.g., anti-itch drugs) used at the start of the screening period, the study drug will be injected into the venous line of the dialysis circuit at the end of each dialysis session for 8 weeks (3 times weekly, 24 times in total). The injected volume of the study drug will be determined based on the subject's dry weight on the day of dosing according to Table 1. If any dialysis circuit trouble precludes injection through the dialysis circuit, it will be permissible to administer the study drug as an intravenous injection. If a fourth dialysis session is extraordinarily required within the week, the study drug will be administered (up to 4 times weekly). If only the extracorporeal ultrafiltration method is used, the study drug will not be administered.

Table 1 Doses

Dry weight	Injected volume	MR13A9 dose			
		0.25 μg/kg group	0.5 μg/kg group	1.0 μg/kg group	Placebo group
< 45.0 kg	0.35 mL	8.75 μg	17.5 μg	35.0 μg	0 μg
≥ 45.0 kg, < 65.0 kg	0.50 mL	12.50 μg	25.0 μg	50.0 μg	0 μg
≥ 65.0 kg, < 85.0 kg	0.70 mL	17.50 μg	35.0 μg	70.0 μg	0 μg
≥ 85.0 kg	0.85 mL	21.25 μg	42.5 μg	85.0 μg	0 μg

3. Follow-up period

A 2-week period after the end of the treatment period or the assessments at discontinuation in the treatment period is defined as the follow-up period, during which subjects will receive no study drug. Subjects will continuously use any restricted concomitant medications (e.g., anti-itch drugs) used at the start of the screening period.

Concomitant Treatments:

1. Concomitant medications

Subjects may use any drug used to treat symptoms of chronic renal failure or drug used to treat complications at the start of the screening period without changing its dosage and administration whenever possible until the end of the follow-up period. It is permissible to change the dosage and administration of any concomitant medication for safety reasons such as the occurrence of adverse events.

2. Restricted concomitant medications

Between the start of the screening period and the end of the follow-up period, subjects may use the drugs listed below that have been used since before the screening period without changing their type or dosage and administration. In addition, do not newly use the drugs listed below:

1) Drugs indicated for the treatment of itching (prescription/nonprescription)
2) Moisturizing drugs (prescription/nonprescription)
3) In-hospital drugs formulated with either of the above
4) Antidepressants, antipsychotics, antiepileptics, hypnotics, anxiolytics, pregabalin, steroids (any route of administration)

Among the drugs listed in 1) to 3) above, topical use of any prescription/nonprescription drug for purposes other than the purpose of treating itching caused by chronic renal failure or any complication of chronic renal failure will not be restricted.

Use of any combination product that contains ingredients indicated for itching but is not indicated itself for itching will not be restricted.

3. Prohibited concomitant medications

Between the start of the screening period and the end of the follow-up period, use of the drugs listed in Table 2 will be prohibited.

Table 2 Prohibited concomitant medications

Class	Common drugs
1) Opioids	nalfurafine hydrochloride, morphine, fentanyl, oxycodone, buprenorphine, pentazocine, codeine phosphate, dihydrocodeine
2) Opioid antagonists	naloxone hydrochloride, eptazocine hydrobromide, naldemedine tosylate
3) Investigational products other than MR13A9	Various kinds

4. Prohibited concomitant therapies

Between the start of the screening period and the end of the follow-up period, use of phototherapy to treat itching will be prohibited.

Hemodialysis Conditions:

Between the start of the screening period and the end of the follow-up period, the hemodialysis method (HD, off-line HDF, on-line HDF, or I-HDF) may not be changed. The dialysis conditions (frequency of dialysis per week, duration of dialysis, dialyzer, vascular access, dialysate flow rate, blood flow rate, and dialysate sodium concentration) should not be changed whenever possible, except for temporary changes with no changes in treatment strategies.

Dependency Assessment: Using the questionnaire shown in Appendix 8, the principal investigator or subinvestigator will rate the dependency on a 4-level scale from “remarkable” to “none”. The dependency assessment members will perform a dependency assessment based on the questionnaire. Details are stipulated in a separate procedure.
Investigations, Observations, Tests, and Evaluations and their Schedules: See the study schedule table.
Sample Size: This study will enroll a total of 240 subjects: 60 for each MR13A9 dose group and the placebo group.

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List of Abbreviations and Terms

Abbreviation/Term	Definition
AUC_{last}	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
AUC_{0-x}	Area under the plasma concentration-time curve from time zero to x hours
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero extrapolated to infinite time
CYP	Cytochrome P450
C_{max}	Maximum plasma concentration
C_0	Plasma concentration immediately after administration
DBTC	Dibutyltin chloride
EC_{50}	50% effective concentration
ECG	Electrocardiography
FOB	Functional observational battery
HD	Hemodialysis
HDF	Hemodiafiltration
hERG	Human ether-a-go-go related gene
IL-(x)	Interleukin
KOR	κ opioid receptor
LPS	Lipopolysaccharide
MATE	Multidrug and toxin extrusion protein
MIP	Macrophage inflammatory protein
MOR	μ opioid receptor
nor-BNI	Nor-binaltorphimine
NRS	Numerical rating scale
NYHA	New York Heart Association
PGIC	Patient Global Impression of Change
QOL	Quality of life
$t_{1/2}$	Terminal-phase elimination half-life
T_{max}	Time to reach peak concentration
TNF	Tumor necrosis factor
UGT	UDP-glucuronosyltransferase
VAS	Visual analog scale

1. Rationale and Background for the Investigational Plan

1.1 Pruritus in Hemodialysis Patients

Pruritus is a common symptom in patients with chronic renal failure receiving hemodialysis treatment. In Japan, approximately 35% of hemodialysis patients are distressed by moderate or severe pruritus.[1)] In hemodialysis patients, pruritus can occur anywhere on the body, causing widespread, symmetric, intermittent itching. Itching is most prominent at night in general, and it deprives patients with more severe pruritus of about 2 hours of sleep on average.[2)] It has been reported that decreased sleep quality and fatigue occur more frequently by 1.9 to 3.7 times and 2.2 to 5.8 times, respectively, in patients with moderate to severe pruritus than in patients with no pruritus, and that the risk of death is 22% higher in patients with moderate to severe pruritus than in patients with no pruritus.[3)] Thus, pruritus in hemodialysis patients affects their physical and mental health by causing sleep disorder and depression, reduces their QOL markedly, and increases their risk of death.

The cause of pruritus in hemodialysis patients is not well understood, and this condition is considered intractable. The development of pruritus involves multiple factors, which include dry skin, accumulation of endogenous substances, and overproduction of chemical mediators such as histamine and substance P.[4),5)] Other possible causes of pruritus include altered immune function and collapsed opioid balance. Opioid receptors are divided into 3 subtypes involved in the regulation of pain and itching signals (μ, κ, and δ). The μ opioid receptor (MOR) binds to β-endorphin and inhibits pain and induces itching, and the κ opioid receptor (KOR) binds to dynorphin and inhibits pain and itching.[6)-8)] In dialysis patients with pruritus, the μ opioid system that induces itching is believed to be predominant over the κ opioid system that inhibits itching.[9),10)]

1.2 Treatment of Pruritus in Hemodialysis Patients

Main treatments of pruritus in hemodialysis patients include topical therapy with moisturizers, such as milky lotion and cream, and with steroids, and topical or internal therapy with antihistamines and antiallergics.[11)] However, many patients have an inadequate response to these existing treatments such as topical and internal therapies, and these patients are treated with an oral KOR agonist, nalfurafine hydrochloride. This drug activates KOR in the central nervous system, thereby exerting antipruritic effects on pruritus refractory to existing treatments. Nalfurafine hydrochloride is effective in treating pruritus; however, because of the oral formulation, dialysis patients have to take a larger number of tablets, which increases the burden of these patients taking many oral drugs to treat their complications. In addition, dialysis patients may have difficulty in taking this drug because of their decreased salivary secretion and restricted fluid intake. Furthermore, nalfurafine hydrochloride activates KOR in the central nervous system and the gastrointestinal tract, thereby inducing adverse drug reactions, such as sleep loss and constipation, frequently.[12)]

Under these circumstances, patients with an inadequate response to existing treatments have hoped the development of a new treatment that relieves itching, is more convenient for use, and causes fewer adverse drug reactions.

1.3 History of the Development of MR13A9

MR13A9 (non-Japanese investigational product code: CR845), a novel peptide KOR agonist developed by Cara Therapeutics, Inc. in the United States, is under development as an

injectable formulation and an oral formulation to relieve pain and pruritus. In Japan, Maruishi Pharmaceutical Co., Ltd. and Kissei Pharmaceutical Co., Ltd. have jointly undertaken its development as an injectable formulation to relieve pruritus. MR13A9 has been designed to activate KOR in peripheral nerves and immune cells, thereby relieving visceral and inflammatory pain and itching and regulating inflammatory signals. MR13A9, which has potent agonist effects on human and rodent KOR, is expected to be effective in treating pruritus based on the results of identification of its pharmacological class and animal experiments. In addition, MR13A9 is expected to be safer and more tolerable than existing KOR agonists because of the limited membrane permeability and central nervous system penetration as indicated by its physicochemical properties. Furthermore, MR13A9 is expected to enhance the quality of pharmaceutical management that includes treatment compliance, treatment instructions, and remaining drug check because it is an injectable formulation administered directly from the dialysis circuit at the end of each dialysis session without fail under the supervision of a physician.

Being expected to become a treatment of pruritus in hemodialysis patients from nonclinical study results, MR13A9 was evaluated in a phase I clinical study in healthy Japanese adults and a clinical pharmacology study in hemodialysis patients in Japan. A subsequent phase II clinical study in hemodialysis patients suggested that MR13A9 relieves pruritus; therefore, this late phase II clinical study has been planned to determine dose-response relationships.

Outside Japan, phase I clinical studies were conducted in healthy adults, patients with impaired renal function, patients with end-stage renal disease, and recreational drug users, which were followed by a phase II clinical study in hemodialysis patients with moderate to severe pruritus. A phase III clinical study in hemodialysis patients with moderate to severe pruritus is ongoing currently.

1.3.1 Nonclinical study results

In *in vitro* primary pharmacodynamic studies, MR13A9 showed an EC_{50} of 0.048 and 0.16 nmol/L against mouse and human KOR, respectively, and did not have any effects on human MOR or human δ opioid receptors at levels up to 10 μmol/L. These results suggested that MR13A9 is a KOR-specific full agonist. At levels up to 10 μmol/L, MR13A9 exhibited no affinity for human or rodent receptors, enzymes, transporters, or ion channels, other than KOR.

In *in vivo* primary pharmacodynamic studies, MR13A9 showed dose-dependent antipruritic effects on mouse models of histamine-induced pruritus, substance P-induced pruritus, compound 48/80-induced pruritus through mast cell stimulations, and guanidinonaltrindole-induced pruritus through KOR inhibition. MR13A9 dose-dependently reduced the release of TNFα induced by LPS in mice and also reduced the release of IL-1β, IL-2, MIP-1β, and IL-12 (p40/p70) in mice. In addition, MR13A9 dose-dependently reduced paw edema in a rat carrageenan-induced paw edema model. These results suggested that MR13A9 has anti-inflammatory effects.

Safety pharmacology studies of MR13A9 showed the following findings. With respect to the central nervous system effects of MR13A9, a functional observational battery study in rats revealed a sedation-like effect in all treatment groups (1, 5, and 25 mg/kg iv), but this effect was not dose-dependent and resolved at 48 hours after administration. In a rotarod study in rats, motor coordination was affected in animals given ≥ 3 mg/kg. With respect to its cardiovascular effects, inhibition of hERG potassium channel current was 7.2% even at 1 mmol/L. In a telemetry study in conscious monkeys, animals exhibited decreases in blood

pressure, body temperature, and pulse rate as well as lethargy and hunchback posture. MR13A9 did not affect any ECG parameters.

With respect to organ and tissue concentrations of MR13A9, a study of radioactivity tissue distribution following repeated intravenous doses in rats showed that the radioactivity was eliminated from the plasma in a biphasic manner. Radioactivity distribution was prominent in the renal medulla and cortex and minimal in the central nervous system.

With respect to its drug interaction, MR13A9 did not inhibit the metabolism of CYP, UGT, or renal excretion transporters (MATE1 and MATE2K), suggesting that it does not serve as their substrate. MR13A9 was therefore considered less likely to cause drug interactions via these isoforms and transporters.

In a 26-week repeated intravenous dose toxicity study of MR13A9 in rats, animals receiving ≥ 0.25 mg/kg/day exhibited decreased locomotor activity, staggering gait, abducted forelimbs, and decreases in body weight and food consumption, all of which were transient changes observed in early weeks of treatment. Histopathological examination revealed proximal tubular basophilic degeneration, seminiferous tubule atrophy, and epididymal intraluminal cell debris in male animals receiving 25 mg/kg/day. The no-observed-adverse-effect level was 2.5 mg/kg/day in males and 25 mg/kg/day in females. A 39-week repeated intravenous dose toxicity study of MR13A9 in monkeys showed the following findings: sedation, somnolence, decreased locomotor activity, and vomiting in animals receiving ≥ 0.25 mg/kg/day; lethargy in male animals receiving 1 mg/kg/day; decreased body weight in animals receiving 1 mg/kg/day; and decreases in food consumption and urine volume in animals receiving ≥ 0.06 mg/kg/day. All of these were transient changes observed in early weeks of treatment. The no-observed-adverse-effect level was ≥ 1 mg/kg/day in both males and females.

The reproductive toxicity of MR13A9 was investigated in a study on fertility and early embryonic development to implantation in rats, studies on embryo-fetal development in rats and rabbits, and a study on pre- and postnatal development, including maternal function, in rats. None of these studies revealed potentially MR13A9–related abnormalities in early embryonic development, embryo-fetal development, maternal animals, pups (F_1), or fetuses (F_2).

The genotoxicity of MR13A9 was investigated in a bacterial reverse mutation test, a chromosomal aberration test with cultured mammalian cells, and a mouse micronucleus test. None of these tests revealed findings suggestive of its genotoxicity.

The carcinogenicity of MR13A9 is being investigated in animals. The development of malignancies in animals given MR13A9 has not been reported to date.

1.3.2 Clinical study results

1.3.2.1 Clinical pharmacology studies

In a clinical pharmacology study in Japanese hemodialysis patients (MR13A9-2), plasma MR13A9 concentrations after the first and third intravenous doses showed a biphasic elimination pattern: a rapid initial phase and a slow elimination phase. After the first dose, C_{max} was 4.38 ± 1.31 and 8.95 ± 2.24 ng/mL and $AUC_{0-\infty}$ was 97.38 ± 35.02 and 240.05 ± 87.23 hr•ng/mL in the 0.5 and 1 μg/kg groups, respectively. After the third dose, C_{max} was 5.38 ± 1.84 and 8.69 ± 2.45 ng/mL and $AUC_{0-\infty}$ was 151.34 ± 48.55 and 316.85 ± 106.67 hr•ng/mL in the 0.5 and 1 μg/kg groups, respectively, showing increases in C_0, C_{max}, AUC_{last}, $AUC_{0-\infty}$, and AUC_{0-48} with increasing dose. T_{max} occurred at the first

sampling time, except for 1 patient receiving 0.5 μg/kg. $t_{1/2}$ was 34.1 to 39.0 hours after the first dose and 40.0 to 49.3 hours after the third dose. The accumulation ratio of Day 5 to Day 1 calculated using the C_{max}, AUC_{0-48}, and trough values indicated a low likelihood of accumulation of MR13A9.

In a clinical pharmacology study in healthy Japanese subjects (MR13A9-1), the cumulative urinary excretion rate became almost constant by 36 hours after the initial dose (i.e., 15 hours after the final dose). The cumulative urinary excretion rate for up to 72 hours after the initial dose (i.e., 51 hours after the final dose) ranged from 71.6% to 76.8%, being similar across the dose groups (1.0, 3.0, 5.0, 10, 20, and 40 μg/kg).

In a clinical pharmacology study in non-Japanese hemodialysis patients (CR845-CLIN1003), postdialysis plasma concentrations of MR13A9 decreased by 75% to 80% on average down below 2 ng/mL on average in all treatment groups (1, 3, and 6 μg/kg). These results suggested that unchanged MR13A9 is eliminated primarily through the kidneys.

1.3.2.2 Efficacy and safety

In a Japanese phase II clinical study (MR13A9-3), 105 previously treated hemodialysis patients with pruritus received intravenous doses of MR13A9 0.25, 0.5, 1.0, or 1.5 μg/kg, or placebo 3 times weekly for 2 weeks. With respect to efficacy, the primary endpoint of change in VAS (i.e., change based on the larger VAS value either in the morning or the evening during the 7 days, the latter half of the treatment period) (mean ± standard deviation) was 23.4 ± 20.0 mm, 28.0 ±18.2 mm, 32.8 ± 25.4 mm, and 41.2 ± 22.8 mm in the 0.25, 0.5, 1.0, and 1.5 μg/kg groups, respectively, versus 26.4 ± 22.3 mm in the placebo group. These results suggested a dose-dependent improvement by treatment with MR13A9 at doses ≥ 0.5 μg/kg. With respect to safety, the incidence of adverse drug reactions was 23.8% (5/21 subjects), 33.3% (7/21 subjects), 61.9% (13/21 subjects), 47.4% (9/19 subjects), and 82.6% (19/23 subjects) in the placebo, 0.25, 0.5, 1.0, and 1.5 μg/kg groups, respectively. Commonly reported adverse drug reactions (in ≥ 10% of subjects in any of the MR13A9 groups) included blood thyroid stimulating hormone decreased, dizziness, blood prolactin increased, nausea, feeling abnormal, and somnolence. The incidence of these adverse drug reactions was as follows: blood thyroid stimulating hormone decreased, 9.5% (2/21 subjects) in the 0.25 μg/kg group, 31.6% (6/19 subjects) in the 1.0 μg/kg group, and 30.4% (7/23 subjects) in the 1.5 μg/kg group; dizziness, 4.8% (1/21 subjects) in the 0.25 μg/kg group, 9.5% (2/21 subjects) in the 0.5 μg/kg group, 10.5% (2/19 subjects) in the 1.0 μg/kg group, and 17.4% (4/23 subjects) in the 1.5 μg/kg group; blood prolactin increased, 4.8% (1/21 subjects) in the 0.25 μg/kg group, 4.8% (1/21 subjects) in the 0.5 μg/kg group, 5.3% (1/19 subjects) in the 1.0 μg/kg group, and 17.4% (4/23 subjects) in the 1.5 μg/kg group; nausea, 4.8% (1/21 subjects) in the 0.25 μg/kg group and 17.4% (4/23 subjects) in the 1.5 μg/kg group; feeling abnormal, 4.8% (1/21 subjects) in the 0.5 μg/kg group and 17.4% (4/23 subjects) in the 1.5 μg/kg group; and somnolence, 4.8% (1/21 subjects) in the 0.25 μg/kg group, 4.8% (1/21 subjects) in the 0.5 μg/kg group, and 13.0% (3/23 subjects) in the 1.5 μg/kg group.

Reported serious adverse events included the following: 2 events (encephalopathy and shunt stenosis) in 2 subjects in the 0.25 μg/kg group, 8 events (abdominal distension, influenza, diverticulitis, dizziness, hyperglycaemia, cholecystitis, hypotension, and muscular weakness) in 4 subjects in the 0.5 μg/kg group, and 1 event (dizziness) in 1 subject in the 1.5 μg/kg group. Of these events, relationship to study treatment was not ruled out for 4 events (diverticulitis, dizziness, hypotension, and hyperglycaemia) in 3 subjects in the 0.5 μg/kg group and 1 event (dizziness) in 1 subject in the 1.5 μg/kg group. Study treatment was discontinued or interrupted due to 1 event in 1 subject in the 0.25 μg/kg group, 2 events in

2 subjects in the 0.5 μg/kg group, 1 event in 1 subject in the 1.0 μg/kg group, and 17 events in 10 subjects in the 1.5 μg/kg group. Dependency was assessed as being present in 2 subjects in the placebo group and 1 subject in the MR13A9 0.5 μg/kg group.

In a non-Japanese phase II clinical study (CR845-CLIN2005 Part B), 65 hemodialysis patients with moderate to severe pruritus received intravenous doses of MR13A9 1.0 μg/kg or placebo 3 times weekly for 2 weeks. With respect to efficacy, the primary endpoint of change in VAS (i.e., change from baseline in the mean VAS for the most intense itching at Week 2) (mean ± standard deviation) was −33.1 ± 23.03 mm in the 1.0 μg/kg group versus −21.5 ± 24.79 mm in the placebo group. With respect to safety, the incidence of adverse drug reactions was 9.4% (3/32 subjects) in the placebo group and 18.2% (6/33 subjects) in the 1.0 μg/kg group. Commonly reported adverse drug reactions (in ≥ 5% of subjects in the MR13A9 group) included dizziness, hypoaesthesia, and pruritus.

In a non-Japanese phase II clinical study (CR845-CLIN2101), 174 hemodialysis patients with moderate to severe pruritus received intravenous doses of MR13A9 0.5, 1.0, or 1.5 μg/kg, or placebo 3 times weekly for 8 weeks. With respect to efficacy, the primary endpoint of change in NRS (i.e., change from baseline in the mean itch NRS at Week 8) (mean ± standard deviation) was −3.9 ± 2.48, −2.8 ± 2.24, and −3.3 ± 2.18 in the 0.5, 1.0, and 1.5 μg/kg groups, respectively, versus −1.9 ± 2.29 mm in the placebo group. With respect to safety, the incidence of adverse drug reactions was 2.2% (1/45 subjects), 27.3% (12/44 subjects), 26.8% (11/41 subjects), and 22.7% (10/44 subjects) in the placebo, 0.5, 1.0, and 1.5 μg/kg groups, respectively. Commonly reported adverse drug reactions (in ≥ 5% of subjects in any of the MR13A9 groups) included dizziness, somnolence, headache, paraesthesia, fatigue, and hyperglycaemia.

1.4 Summary of Expected Adverse Drug Reactions and Benefits

1.4.1 Expected adverse drug reactions

In a phase II clinical study in Japanese hemodialysis patients (MR13A9-3), 84 subjects received intravenous doses of MR13A9 0.25, 0.5, 1.0, or 1.5 μg/kg 3 times weekly for 2 weeks. Adverse drug reactions reported in ≥ 10% of subjects in any of the MR13A9 groups included blood thyroid stimulating hormone decreased, dizziness, blood prolactin increased, nausea, feeling abnormal, and somnolence. Although adverse drug reactions suggesting the effects of MR13A9 on the central nervous system tended to occur relatively frequently, most of them were mild and none of them were severe in severity.

In a phase II clinical study in non-Japanese hemodialysis patients (CR845-CLIN2005 Part B), 33 subjects received intravenous doses of MR13A9 1.0 μg/kg 3 times weekly for 2 weeks. Adverse drug reactions reported in ≥ 5% of subjects receiving MR13A9 included dizziness and hypoaesthesia. In a phase II clinical study in non-Japanese hemodialysis patients (CR845-CLIN2101), 129 subjects received intravenous doses of MR13A9 0.5, 1.0, or 1.5 μg/kg 3 times weekly for 8 weeks. Adverse drug reactions reported in ≥ 5% of subjects in any of the MR13A9 groups included dizziness, somnolence, headache, paraesthesia, fatigue, and hyperglycaemia.

In non-Japanese clinical studies, an adverse event of serum sodium increased associated with the aquaretic effect of KOR agonists[13)] was reported in subjects receiving ≥ 5 μg/kg. In addition, an adverse event of tachycardia associated with the same effect was reported. In a phase I clinical study in healthy Japanese adult males (MR13A9-1), blood sodium increased was reported in 4 of 6 subjects in the 5.0 μg/kg group during the repeated-dose period. These

events were reported only in clinical studies in subjects with normal renal function and have not been reported in clinical studies in hemodialysis patients.

1.4.2 Expected benefits

The Japanese and non-Japanese phase II clinical studies in hemodialysis patients with pruritus have suggested the efficacy of MR13A9 for pruritus in hemodialysis patients. Treatment with MR13A9 is also expected to relieve pruritus in hemodialysis patients in the present study.

2. Study Title and Development Phase

2.1 Title of Study

A phase II clinical study of MR13A9 in previously treated hemodialysis patients with pruritus

(Protocol No.: MR13A9-4)

2.2 Development Phase

Phase II

3. Study Objectives

To determine the dose-response relationship for the efficacy, safety, and pharmacokinetics of MR13A9 0.25, 0.5, or 1.0 μg/kg administered to previously treated hemodialysis patients with pruritus for 8 weeks in a placebo-controlled, double-blind design.

3.1 Endpoints for Efficacy

3.1.1 Efficacy endpoints

1) Primary endpoint

- Itch NRS score (The primary variable is change from baseline in the mean NRS score at Week 8 of the treatment period)

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

2) Secondary endpoints

- Itch score based on the Shiratori's severity criteria[14)]
- Skindex-16 score[15)]
- 5-D itch scale score[16)]
- Patient Global Impression of Change (PGIC)

3.1.2 Rationale for the efficacy endpoints

1) Primary endpoint

The itch NRS score has been selected as the primary endpoint because it is used widely as a pruritus assessment method in clinical studies[2)] and is also used as the primary endpoint of the non-Japanese phase III clinical study.

2) Secondary endpoints

- The Shiratori's severity criteria have been selected as an endpoint for pruritus, provided that they are used widely to assess the degree of itching by dermatologists in Japan and that they can also be used to assess sleep disorder because they use the effects on daily activities as the criteria for severity.
- Skindex-16 and 5-D itch scale have been selected as QOL endpoints for pruritus because they are used to assess the skin disease-related QOL.
- PGIC has been selected as an endpoint for treatment effects assessed by subjects.

3.2 Endpoints for Safety

3.2.1 Safety endpoints

- Occurrence of adverse events
- Occurrence of adverse drug reactions
- Occurrence of adverse events of special interest
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Vital signs (blood pressure, pulse rate, body temperature)
- Body weight
- 12-lead electrocardiography (ECG)
- Dependency assessment

3.2.2 Rationale for the safety endpoints

In addition to the endpoints generally used for safety evaluation, endocrinology testing and dependency assessment have been selected because these endpoints could be affected by opioids. In addition, for careful assessment of their effects on the central nervous system, adverse events of special interest have been established.

3.3 Endpoints for Pharmacokinetics

3.3.1 Pharmacokinetic endpoint

- Plasma concentration of MR13A9 (unchanged drug)

3.3.2 Rationale for the pharmacokinetic endpoint

This endpoint has been established to determine the pharmacokinetic dose-response relationship in Japanese hemodialysis patients with pruritus.

4. Study Population

This study will enroll previously treated hemodialysis patients with pruritus who meet all of the inclusion criteria and none of the exclusion criteria below.

4.1 Inclusion Criteria

4.1.1 Inclusion criteria

1) Patients aged 20 years or older (at the time of signing informed consent)
2) Japanese patients providing written informed consent for study participation in person (Their first- and second-degree relatives must be all Japanese)
3) Patients with chronic renal failure on periodic hemodialysis (HD, off-line HDF, on-line HDF, or I-HDF) 3 times weekly for ≥ 12 weeks prior to the informed consent procedure who can continue hemodialysis without changing its frequency or method (excluding temporary changes with no changes in treatment strategies) during the study
4) Patients whose pruritus treatment for 1 year prior to the informed consent procedure

meets either (1) or (2) below:

(1) Drug therapy with nalfurafine hydrochloride for ≥ 2 consecutive weeks

(2) Inadequate response to both drug therapies a) and b) below:

a) Systemic (e.g., oral, injection) therapy with antihistamines or antiallergics contained in prescription drugs indicated for the treatment of itching for ≥ 2 consecutive weeks

b) Local (topical) therapy with prescription drugs indicated for the treatment of itching or moisturizers prescribed by physicians

5) Patients not receiving nalfurafine hydrochloride for ≥ 2 weeks prior to the start of the screening period

6) Patients whose pruritus has been treated with 1 or more drugs listed below since prior to the start of the screening period:

- Drugs indicated for the treatment of itching (prescription/nonprescription) (excluding nalfurafine hydrochloride)
- Moisturizing drugs (prescription/nonprescription)
- Products formulated with either of the above

7) Patients whose NRS score in the 7 days prior to the start of the treatment period (including the score recorded on the day at Week 0) meets both of the below:

- NRS scores have been recorded for ≥ 5 days.
- The mean value of the recorded scores exceeds 4.

8) Patients whose itch score based on the Shiratori's severity criteria in the 7 days prior to the start of the treatment period (including the score recorded on the day at Week 0) meets both of the below:

- Itch scores during the day and the night have been recorded for ≥ 5 days.
- The larger itch score either during the day or the night is "3. Moderate itching" or greater for ≥ 2 days.

9) Patients who can record the symptom diary, as instructed by the principal investigator, subinvestigator, or clinical research coordinator

4.1.2 Rationale for the inclusion criteria

1) To include patients old enough to provide consent in person legally.

2) To comply with the ethical principles that have their origin in the Declaration of Helsinki and GCP.

3) To include patients on stable hemodialysis.

4) To include patients whose pruritus has been treated with drug therapy and who have had an inadequate response to the drug therapy other than nalfurafine hydrochloride. Patients previously treated with nalfurafine hydrochloride will be included because it is assumed that they have not responded to drugs other than nalfurafine hydrochloride.

5) To exclude the effects of nalfurafine hydrochloride on the efficacy and safety of MR13A9.

6)-8) To include patients who have a certain degree of itching continuously.

9) To include patients who can perform appropriate assessment using a symptom diary.

4.2 Exclusion Criteria

4.2.1 Exclusion criteria

1) Patients with itching caused by conditions other than chronic renal failure or complications of chronic renal failure, which could affect the efficacy evaluation in the opinion of the principal investigator or subinvestigator (e.g., atopic dermatitis, chronic urticaria)

2) Patients with concurrent hepatic cirrhosis

3) Patients who received phototherapy to treat itching within 4 weeks prior to the start of the screening period

4) Patients who previously received any study drug (including placebo) in a clinical study of MR13A9

5) Patients with any concurrent or previous disease that could affect the evaluations in this study in the opinion of the principal investigator or subinvestigator

6) Patients with any adverse drug reaction to nalfurafine hydrochloride in the past who are ineligible for study participation in the opinion of the principal investigator or subinvestigator

7) Patients with drug hypersensitivity to opioids

8) Patients whose laboratory data at the start of the screening period meet any of the criteria (1) to (3) below:

   (1) ALT > 2.5 times the upper limit of normal

   (2) AST > 2.5 times the upper limit of normal

   (3) Total bilirubin > 2 times the upper limit of normal

9) Patients whose dry weight is < 24 kg at the start of the screening period

10) Patients with congestive heart failure (NYHA functional class IV) (Appendix 1)

11) Patients with concurrent malignancy or a history of malignancy within 5 years prior to the informed consent procedure

12) Patients with concurrent or previous drug abuse (defined as illicit drug use)

13) Patients with concurrent or previous alcoholism

14) Patients with a history of severe drug hypersensitivity

15) Patients with mental disorder (i.e., depression, schizophrenia, or dementia) that could affect the evaluation of the investigational product

16) Female patients who are pregnant, breastfeeding, intending to become pregnant between the informed consent procedure and the end of the follow-up period, or unwilling to use appropriate methods to prevent conception

17) Male patients who are unwilling to use appropriate methods to prevent conception between the start of study treatment and 12 weeks after the day of the final dose

18) Patients who received treatment with any study drug or medical device in a clinical study (including clinical studies of medical devices) within 12 weeks prior to the informed consent procedure, or who are planning to participate in another clinical study before the end of the follow-up period of this study

19) Patients scheduled to be hospitalized to receive any medical intervention between the informed consent procedure and the end of the follow-up period

20) Patients withdrawn from the study in the screening period because they are found not meeting either of inclusion criteria 7) or 8) after participation in the study

21) Patients withdrawn from the study in the screening period after re-registration

22) Other patients ineligible for study participation in the opinion of the principal investigator or subinvestigator

4.2.2 Rationale for the exclusion criteria

1)-5)	To perform the efficacy evaluation of MR13A9 appropriately.
6)-8), 10)-14), 19), 22)	To ensure the safety of subjects.
9)	To prevent the dose of the investigational product from exceeding the prespecified dose.
15)	To exclude the effect of this condition on protocol adherence.
16), 17)	To ensure the safety of pregnant women, fetuses, and infants because the safety of MR13A9 in them has not been established.
18)	To establish a certain time interval for subjects, between administration of another study drug and administration of MR13A9 because it is impossible to rule out the possibility of an interaction between these drugs and the development of delayed adverse reactions of another investigational product as well as it is necessary to do so from the ethical aspect.
20), 21)	Re-registration will not be permitted because it could affect the efficacy evaluation.

4.3 Discontinuation of Individual Subjects

4.3.1 Discontinuation criteria (discontinuation of individual subjects)

1) Adverse event (The name of the adverse event should be recorded in the case report form):

- It is necessary to withdraw the subject from the study because of the adverse event in the opinion of the principal investigator or subinvestigator
- The subject does not want to continue the study due to the adverse event

2) Lack of efficacy (inadequate response):

- Study continuation may cause an unacceptable risk to the subject because of the lack of efficacy of the study drug in the opinion of the principal investigator or subinvestigator

3) Voluntary request for study discontinuation by the subject (Discontinuation due to an adverse event is categorized as 1) above and discontinuation due to the lack of efficacy is

categorized as 2) above)

4) Significant protocol deviation during the study
   - Any GCP violation is found
   - After registration, the subject is found not meeting any of the inclusion criteria or meeting any of the exclusion criteria stipulated in the protocol
   - Study continuation may cause injury to the subject because of the subject's protocol noncompliance in the opinion of the principal investigator or subinvestigator
5) Four consecutive missed doses of the study drug
6) Pregnancy
7) Discontinuation of the entire study
8) Discontinuation of the study at the study site
9) Lost to observation or follow-up
   - Study continuation becomes impossible because of failure to contact the subject
10) Any other cases where it is necessary to withdraw the subject from the study in the opinion of the principal investigator or subinvestigator (A detailed reason should be recorded in the case report form)

4.3.2 Responses to the discontinuation of any individual subject

If a subject meets any of the criteria described in "4.3.1 Discontinuation criteria (discontinuation of individual subjects)" during the study, the principal investigator or subinvestigator will immediately decide to discontinue the study. On the day of dialysis after the decision to discontinue, the prespecified assessment items at discontinuation will be measured and assessed and the date of discontinuation and the reason for discontinuation will be recorded in the case report form. The date of discontinuation will be the day when the principal investigator or subinvestigator decides to discontinue the study.

If the study is discontinued because of the occurrence of an adverse event, the principal investigator or subinvestigator will promptly provide appropriate treatment for the subject and perform a follow-up investigation, as instructed in "9.12.9 Follow-up investigation"

If the study is discontinued during the treatment period, the next day of the assessments at discontinuation will be regarded as the start date of the follow-up period.

4.3.3 Investigation of subjects not returning to the study site

If a subject fails to return to the study site as scheduled, the principal investigator, subinvestigator, or clinical research coordinator will immediately investigate the reason for missed visits and the subsequent course.

5. Subject Consent

5.1 Timing of Informed Consent

Written informed consent must be obtained before the start of the screening period (before any protocol-specified testing, and before the start of washout for patients on nalfurafine hydrochloride).

5.2 Informed Consent Procedure

The principal investigator will prepare written information and consent forms with reference to the materials and information necessary to prepare these documents provided by the sponsor (e.g., examples of written information and informed consent forms), and obtain approval of the institutional review board (IRB).

The principal investigator or subinvestigator will select subjects who have sufficiently considered the objectives of the study from the ethical and scientific standpoints. Individuals incapable of giving consent will not be selected as subjects. When selecting an individual who may have an unreasonable disadvantage because he/she does not participate in the study, the principal investigator or subinvestigator must ensure that consent is given voluntarily by the subject.

Prior to the participation of each subject in the study, the principal investigator or subinvestigator will provide the subject with a thorough explanation using the written information. The principal investigator or subinvestigator will obtain voluntary written consent for study participation (informed consent form) from the subject after giving a chance to ask questions, answering to the questions sufficiently, and confirming that the subject has understood the information sufficiently. The informed consent form will be dated and signed (or affix name and seal) by the principal investigator or subinvestigator giving the explanation and dated and signed by the subject. Any clinical research coordinator giving a supplementary explanation will also date and sign (or affix name and seal) the informed consent form.

The principal investigator or subinvestigator will hand the written information and a copy of the informed consent form to the subject and retain the original informed consent form at the study site.

6. Study Drugs

6.1 Test Drug and Control Drug

6.1.1 Test drug

1) Code name: MR13A9
2) Nonproprietary name: Difelikefalin (INN)
3) Strength and dosage form:
   - MR13A9 0.025 mg/mL (injection): Each vial contains 1.3 mL of MR13A9 dissolved in 0.04 mol/L isotonic acetate buffer (pH 4.5) at a concentration of 0.025 mg/mL.
   - MR13A9 0.05 mg/mL (injection): Each vial contains 1.3 mL of MR13A9 dissolved in 0.04 mol/L isotonic acetate buffer (pH 4.5) at a concentration of 0.05 mg/mL.
   - MR13A9 0.1 mg/mL (injection): Each vial contains 1.3 mL of MR13A9 dissolved in 0.04 mol/L isotonic acetate buffer (pH 4.5) at a concentration of 0.1 mg/mL.
4) Storage conditions: Store at room temperature (1°C to 30°C)

6.1.2 Control drug

1) Strength and dosage form:

MR13A9 placebo (injection): Each vial contains 1.3 mL of 0.04 mol/L isotonic acetate buffer

(pH 4.5).

The MR13A9 placebo is indistinguishable from MR13A9 0.025, 0.05, or 0.1 mg/mL.

2) Storage conditions: Store at room temperature (1°C to 30°C)

6.1.3 Rationale for the control drug

With reference to the "Choice of Control Group and Related Issues in Clinical Trials" (MHLW PFSB/ELD Notification No. 136 dated February 27, 2001), a placebo has been selected as a control drug to control all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the test drug (natural history of the disease, subject or investigator expectations, the effect of being in a trial, use of other therapy, and subjective elements of diagnosis or assessment).

6.2 Packaging of the Study Drugs

A total of 27 vials of MR13A9 0.025, 0.05, 0.1 mg/mL, or placebo (24 vials for 8 weeks + 3 spare vials) will be packed in 1 carton to prepare a carton per subject.

6.3 Labeling (Samples)

For investigational use

MR13A9

Drug Number

Storage: Store at room temperature (1°C to 30°C)
Serial No.: E8181

Kissei Pharmaceutical Co., Ltd.

Figure 6.3-1 Vial Label

For investigational use

MR13A9

Drug Number

Storage: Store at room temperature (1°C to 30°C)
Serial No.: E8181

Kissei Pharmaceutical Co., Ltd.
Clinical Development
3-1-3 Koishikawa, Bunkyo-ku, Tokyo
Tel: 03-5684-3533

Subject Identification Code

Figure 6.3-2 Carton label

6.4 Management of the Study Drugs

The study drug manager will manage and store the study drugs appropriately, as stipulated

separately in the written procedure.

7. Study Methods

7.1 Study Design

A placebo-controlled, multicenter, randomized, double-blind, parallel-group study

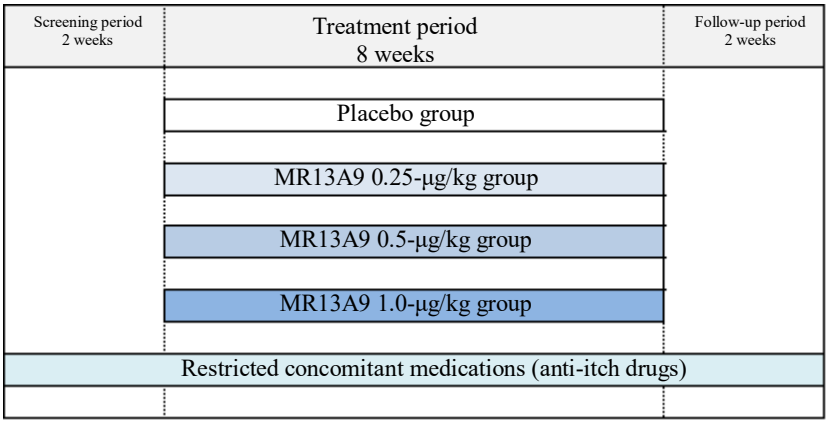

Figure 7.1-1 Study Design

7.2 Doses and Dosing Method

7.2.1 Screening period

A 2-week period before entry into the treatment period is defined as the screening period, during which subjects will receive no study drug. Subjects will continuously use any restricted concomitant medications (e.g., anti-itch drugs) used at the start of the screening period.

7.2.2 Treatment period

In addition to the use of restricted concomitant medications (e.g., anti-itch drugs) used at the start of the screening period, the study drug will be injected into the venous line of the dialysis circuit at the end of each dialysis session for 8 weeks (3 times weekly, 24 times in total). The injected volume of the study drug will be determined based on the subject's dry weight on the day of dosing according to Table 7.2.2-1. If any dialysis circuit trouble precludes injection through the dialysis circuit, it will be permissible to administer the study drug as an intravenous injection. If a fourth dialysis session is extraordinarily required within the week, the study drug will be administered (up to 4 times weekly). If only the extracorporeal ultrafiltration method is used, the study drug will not be administered. Details are stipulated in a separate procedure.

Table 7.2.2-1 Doses

Dry weight	Injected volume	MR13A9 dose			
		0.25 µg/kg group	0.5 µg/kg group	1.0 µg/kg group	Placebo group
< 45.0 kg	0.35 mL	8.75 µg	17.5 µg	35.0 µg	0 µg
≥ 45.0 kg, < 65.0 kg	0.50 mL	12.50 µg	25.0 µg	50.0 µg	0 µg
≥ 65.0 kg, < 85.0 kg	0.70 mL	17.50 µg	35.0 µg	70.0 µg	0 µg
≥ 85.0 kg	0.85 mL	21.25 µg	42.5 µg	85.0 µg	0 µg

7.2.3 Follow-up period

A 2-week period after the end of the treatment period or the assessments at discontinuation in the treatment period is defined as the follow-up period, during which subjects will receive no study drug. Subjects will continuously use any restricted concomitant medications (e.g., anti-itch drugs) used at the start of the screening period.

7.2.4 Rationale for the doses

A dose-dependent improvement in itching was suggested in the Japanese phase II clinical study in hemodialysis patients with pruritus receiving MR13A9 0.25, 0.5, 1.0, or 1.5 μg/kg for 2 weeks (MR13A9-3). As for safety, all of these doses were tolerated, but the dose of 1.5 μg/kg was not considered suitable for a clinical dose, taking the occurrence of adverse drug reactions into account. It was thus determined that the efficacy and safety profiles of MR13A9 at 0.25, 0.5, and 1.0 μg/kg would be investigated in detail to determine the recommended clinical doses of MR13A9. For dose selection, body weight categories based on dry weight were established, taking the convenience of drug preparation into account.

In addition, an 8-week period that allows the efficacy evaluation of MR13A9 was established, provided that pruritus associated with hemodialysis requires prolonged treatment and that the improvement in itching was maintained after Week 2 in the non-Japanese phase II clinical study of MR13A9 that was administered for 8 weeks (CR845-CLIN2101).

7.3 Concomitant Treatments

7.3.1 Concomitant medications

Subjects may use any drug used to treat symptoms of chronic renal failure or drug used to treat complications at the start of the screening period without changing its dosage and administration whenever possible until the end of the follow-up period. It is permissible to change the dosage and administration of any concomitant medication for safety reasons such as the occurrence of adverse events.

7.3.2 Restricted concomitant medications

Between the start of the screening period and the end of the follow-up period, subjects may use the drugs listed below that have been used since before the screening period without changing their type or dosage and administration. In addition, do not newly use the drugs listed below:

1) Drugs indicated for the treatment of itching (prescription/nonprescription)
2) Moisturizing drugs (prescription/nonprescription)
3) In-hospital drugs formulated with either of the above
4) Antidepressants, antipsychotics, antiepileptics, hypnotics, anxiolytics, pregabalin, steroids (any route of administration)

Among the drugs listed in 1) to 3) above, topical use of any prescription/nonprescription drug for purposes other than the purpose of treating itching caused by chronic renal failure or any complication of chronic renal failure will not be restricted.

Use of any combination product that contains ingredients indicated for itching but is not indicated itself for itching will not be restricted.

7.3.3 Prohibited concomitant medications

Between the start of the screening period and the end of the follow-up period, use of the drugs listed in Table 7.3.3-1 will be prohibited.

Table 7.3.3-1 Prohibited concomitant medications

Class	Common drugs
1) Opioids	Nalfurafine hydrochloride, morphine, fentanyl, oxycodone, buprenorphine, pentazocine, codeine phosphate, dihydrocodeine
2) Opioid antagonists	Naloxone hydrochloride, eptazocine hydrobromide, naldemedine tosylate
3) Investigational product other than MR13A9	Various kinds

7.3.4 Rationale for the prohibited concomitant medications

1), 2) To exclude their effects on the efficacy evaluation of MR13A9.

3) To exclude their effects when coadministered with MR13A9 on the safety evaluation of MR13A9.

7.3.5 Prohibited concomitant therapies

Between the start of the screening period and the end of the follow-up period, use of phototherapy to treat itching will be prohibited.

7.3.6 Rationale for the prohibited concomitant therapies

To exclude the effect of phototherapy on the efficacy evaluation of MR13A9.

7.4 Hemodialysis Conditions

Between the start of the screening period and the end of the follow-up period, the hemodialysis method (HD, off-line HDF, on-line HDF, or I-HDF) may not be changed. The dialysis conditions (frequency of dialysis per week, duration of dialysis, dialyzer, vascular access, dialysate flow rate, blood flow rate, and dialysate sodium concentration) may not be changed whenever possible, except for temporary changes with no changes in treatment strategies.

7.5 Randomization and Blinding

7.5.1 Treatment Assignment

The person responsible for treatment assignment will prepare a treatment assignment table to assign subjects to MR13A9 0.25, 0.5, or 1.0 μg/kg, or placebo at a ratio of 1:1:1:1.

7.5.2 Preparation of emergency key codes

The person responsible for treatment assignment will prepare emergency key codes to allow immediate identification of the treatment assigned to each subject in emergencies.

7.5.3 Retention of the treatment assignment table and the emergency key codes

The person responsible for treatment assignment will seal the treatment assignment table and the emergency key codes so that blind-breaking can be detected, and retain them until

unblinding, as stipulated separately in the written procedure.

7.5.4 Subject registration

7.5.4.1 Primary subject registration

The principal investigator or subinvestigator will assess the eligibility of all subjects providing consent at the time of signing informed consent (see "4. Study Population"), enter necessary information in a primary subject registration form, and register the subjects by the next day.

The subject registration center will notify the principal investigator or subinvestigator about the acceptance or rejection of the primary subject registration for each subject.

The completed primary subject registration form and the primary subject registration confirmation form obtained from the subject registration center will be retained at the study site.

7.5.4.2 Secondary subject registration

The principal investigator or subinvestigator will assess the eligibility of each subject at the start of the screening period (see "4. Study Population"), enter necessary information in a secondary subject registration form, and register the subject by the next day.

The subject registration center will notify the principal investigator or subinvestigator about the acceptance or rejection of the secondary subject registration of each subject.

The completed secondary subject registration form and the secondary subject registration confirmation form obtained from the subject registration center will be retained at the study site.

For any subject eligible for primary registration but ineligible for secondary registration, the principal investigator or subinvestigator will notify the subject registration center about the reason for ineligibility.

7.5.4.3 Tertiary subject registration

The principal investigator or subinvestigator will assess the final eligibility of each subject at the start of the treatment period (see "4. Study Population"), enter necessary information in a tertiary subject registration form, and register the each subject promptly.

The subject registration center will notify the principal investigator or subinvestigator about the acceptance or rejection of the tertiary subject registration of each subject, and the drug number for the subject when the registration of the subject has been accepted. The principal investigator or subinvestigator will prescribe the study drug of the drug number notified by the subject registration center for the subject.

The completed tertiary subject registration form and the tertiary subject registration confirmation form obtained from the subject registration center will be retained at the study site.

For any subject eligible for secondary registration but ineligible for tertiary registration, the principal investigator or subinvestigator will notify the subject registration center about the reason for ineligibility.

7.5.4.4 Randomization of subjects

Based on the treatment assignment table, the subject registration center will randomly assign subjects eligible for tertiary registration to 4 treatment groups by a dynamic allocation method using 2 stratification factors: prior treatment with nalfurafine hydrochloride (for ≥ 2 consecutive weeks in the year prior to the informed consent procedure) and specific signs or symptoms during the screening period (Appendix 2) confirmed before dialysis at Week 0.

7.5.5 Opening of emergency key codes

If the study drug assigned to a subject needs to be identified immediately in emergencies, the emergency key code for the drug number will be opened to identify the treatment, as instructed below:

1) In an emergency, the principal investigator or subinvestigator will promptly provide appropriate treatment for the subject, confirm his/her health condition, and report to the sponsor. If it is considered necessary to open the emergency key code for the subject to assure his/her safety, the principal investigator or subinvestigator will request the sponsor to open the emergency key code by telephone or other means.
2) If requested by the principal investigator or subinvestigator to open the emergency key code or if the sponsor considered necessary to open the emergency key code, the sponsor will open the emergency key code for the drug number, as stipulated separately in the procedure, and report the drug number to the principal investigator.
3) For the subject with the relevant drug number, the principal investigator will complete a case report form and a record of premature opening of a treatment assignment code and submit the documents to the sponsor.

7.5.6 Unblinding

The person responsible for treatment assignment will confirm that the blind has been maintained throughout the study period and then unblind the treatment assignment table.

7.5.7 Maintenance of the blind

To maintain the blind, the results of measurement of plasma drug concentrations will be kept and managed at the measurement organization until the unblinding of the treatment assignment table. Any information that can identify treatment groups or individual subjects will be reported to the sponsor and the study site after the unblinding of the treatment assignment table.

7.6 Sample Size

7.6.1 Sample size

This study will enroll 60 subjects for each MR13A9 dose group and the placebo group, 240 subjects in total.

7.6.2 Rationale for the sample size

In the non-Japanese phase II clinical study (CR845-CLIN2101), the change from baseline in NRS score at Week 8 (mean ± standard deviation) was −3.9 ± 2.48, −2.8 ± 2.24, and −3.4 ± 2.34 in the MR13A9 0.5 μg/kg, 1.0 μg/kg, and combined (CR845 all doses) groups, respectively, versus −1.9 ± 2.29 in the placebo group. The difference in the change from

baseline in NRS score (least squares mean ± standard error) in each of the MR13A9 0.5 μg/kg, 1.0 μg/kg, and combined groups versus the placebo group was −1.8 ± 0.50, −0.8 ± 0.52, and −1.3 ± 0.41, respectively.

For the present study, the MR13A9 0.5 and 1.0 μg/kg groups were assumed to have a similar change in NRS score at Week 8 of the treatment period to that observed in the MR13A9 combined group in the non-Japanese phase II clinical study. The MR13A9 0.25 μg/kg group, for which no efficacy results were obtained, was assumed to have about half the change in NRS score assumed above. The mean difference in NRS score between each of the MR13A9 0.25, 0.5, and 1.0 μg/kg groups and the placebo group was assumed to be −0.6, −1.3, and −1.3, respectively, with a common standard deviation of 2.5. When the dose-response relationship for the MR13A9 0.25, 0.5, and 1.0 μg/kg groups was evaluated using the contrast patterns shown in "13.5.2.1.1 Primary analysis," with a two-sided significance level of 5% and a sample size of 60 subjects per group, a contrast pattern of 3, 1, −2, −2 (placebo, 0.25, 0.5, 1.0 μg/kg) produced a statistical power of 91.7%. Statistical power is more than 80% when the MR13A9 0.5 or 1.0 μg/kg group (60 subjects per groups) was compared with the placebo group.

With respect to the mean difference in NRS score at Week 2 of the treatment period, the MR13A9 0.5 and 1.0 μg/kg groups were assumed to show a difference considered clinically meaningful versus the placebo group, and the MR13A9 0.25 μg/kg group was assumed to show about half the difference above. The mean difference in NRS score versus the placebo group was assumed to be −0.4, −0.8, and −0.8 in the MR13A9 0.25, 0.5, and 1.0 μg/kg groups, respectively, with a common standard deviation of 1.9. As with the evaluation of the dose-response relationship at Week 8 of the treatment period, when the dose-response relationship for the MR13A9 0.25, 0.5, and 1.0 μg/kg groups was evaluated using the contrast patterns, with a two-sided significance level of 5% and a sample size of 60 subjects per group, a contrast pattern of 3, 1, −2, −2 (placebo, 0.25, 0.5, 1.0 μg/kg) produced a statistical power of 76.4%.

8. Subject Instructions and Management

The principal investigator or subinvestigator should sufficiently explain the significance and objectives of the study to subjects, and instruct and manage them especially for the following:

1) Confirm the absence of somnolence, dizziness, or similar symptoms after receiving the study drug and return home. Report any symptoms to the principal investigator or subinvestigator. Pay attention during hazardous machine operation and automobile driving during the treatment period. Avoid hazardous machine operation and automobile driving on the day of study treatment.

2) Maintain the symptom diary in subject every day. Record symptoms in the designated form and bring it at visit dates if any electronic diary system trouble makes the maintenance of the symptom diary impossible.

3) Take all prescribed drugs other than the study drug properly as instructed.

4) Be sure to visit the study site as scheduled. Inform the study site in advance if it is impossible to visit for some unavoidable reason. Visit the study site at the same time at every visit whenever possible.

5) Report the drug(s) used currently to the principal investigator or subinvestigator before participation in the study. Consult the principal investigator or subinvestigator before use about any new drug prescribed at other medical departments or hospitals or any over-the-

counter drug to be started. Report to the principal investigator or subinvestigator immediately if it was inevitable to use any drug without consultation.

6) Be sure to report in advance any visit to another department or hospital during the study period to the principal investigator or subinvestigator and report your participation in the study to the doctor at the department or hospital. If it is impossible to report in advance for unavoidable reasons such as an emergency visit, report your participation in the study to the doctor or pharmacist at the department or hospital and immediately report the visit to the department or hospital as well as prescribed drugs and other information to the principal investigator or subinvestigator.

7) Immediately inform the principal investigator or subinvestigator about any abnormalities in your body after undergoing tests at the end of the follow-up period (or at the time of discontinuation) or at the end of the follow-up investigation.

8) Women of childbearing potential must avoid intercourse during the study period or use appropriate contraceptive methods when having intercourse. Immediately inform the principal investigator or subinvestigator about any suspected pregnancy during the study period.

9) Men must avoid intercourse during the study period or use appropriate contraceptive methods when having intercourse. Immediately inform the principal investigator or subinvestigator about any suspected pregnancy of your partner between the start of study treatment and 12 weeks after the final dose.

10) Avoid disclosing any information related to this study, such as data used during the study, adverse events reported during the study, tests performed during the study, and personal remarks about administration of the study drug, on the Internet (e.g., Facebook, Twitter, blogs) or other information media (e.g., newspapers, magazines, advertisements).

9. Investigations, Observations, Tests, and Evaluations

The principal investigator and subinvestigator will perform investigations, observations, tests, and evaluations according to the study schedule (pages 49 and 50) and the respective procedures of investigations, observations, and tests.

9.1 Subject Demographics

The following subject demographics will be investigated and recorded in the case report form:

1) Date of written informed consent

2) Month of birth, sex, race

3) Body height

4) Etiology of chronic renal failure

5) Time when hemodialysis was started

6) Hemodialysis method (HD, off-line HDF, on-line HDF, or I-HDF) and dialysis conditions (frequency of dialysis per week, duration of dialysis, dialyzer, vascular access, dialysate flow rate, blood flow rate, and dialysate sodium concentration)

7) Dry weight at the start of the screening period

8) Medical history (any concurrent disease at the time of signing informed consent); if yes, the name of the disease

9) Time of onset of itching

10) Prior treatment with nalfurafine hydrochloride within 1 year of the time of signing informed consent; if yes, the duration of treatment and dose

11) Remaining renal function

12) Need for pregnancy testing

13) Information related to the inclusion/exclusion criteria

9.2 Treatment Compliance

The principal investigator or subinvestigator will record compliance with study treatment (day of dosing, time of dosing, route of dosing, dry weight on the day of dosing, drug number, and injected volume) in the case report form.

9.3 Concomitant Medications and Concomitant Therapies

9.3.1 Concomitant medications

For all drugs (including over-the-counter drugs, Chinese herbal drugs, vitamins) used between the informed consent procedure and the end of the follow-up period, information on use (drug name, route of administration, duration of use, indication) will be recorded in the case report form. For any change in the drug name, dose, or dosing frequency of restricted concomitant medications, the date, detail, and reason for the change will be recorded in the case report form. The drugs listed below will require no recording in the case report form.

- Drugs used for dialysis (anticoagulants, local anesthetics, disinfectants, physiological saline, dialysate)
- Infusion solution used to establish access
- Diluents for injection
- Vehicles used for in-hospital dispensing (other than drugs of which main effect is expected)
- Pretreatment drugs for tests

9.3.2 Concomitant therapies

If phototherapy to treat itching is performed between the time of signing informed consent and the end of the follow-up period, implementation status of the therapy (name and duration of treatment) will be recorded in the case report form.

9.3.3 Implementation status of dialysis

The dates of dialysis between the start of the screening period and the end of the follow-up period will be recorded in the case report form. For any change in the hemodialysis method (HD, off-line HDF, on-line HDF, or I-HDF), the date, detail, and reason for the change will be recorded in the case report form.

The sponsor will calculate the single-pool Kt/V at the start of the screening period. The single-pool Kt/V will be calculated using the Daugirdas formula.[17)]

9.4 Efficacy Endpoints

9.4.1 Symptom diary (electronic diary)

The principal investigator, subinvestigator, or clinical research coordinator will instruct each subject how to record the symptom diary, as well as register the information on each subject in the electronic diary system to prepare for the start of recording. The subject will record the following information 1) and 2) in the symptom diary from the next day of the start date of the screening period until the end date of the follow-up period.

1) NRS score

Looking back on the period between the time of awakening on the previous day of assessment and the time of awakening on the day of assessment (including sleeping hours) once daily, subjects will assess the NRS score for the most severe itching by themselves and record the score in the symptom diary. According to Appendix 3, the most severe itching within the day will be assessed in integer on a scale ranging from 0 to 10, where 0 represents no itching and 10 represents worst itching imaginable.

2) Shiratori's severity criteria

Looking back on the period between the time of awakening on the previous day of assessment and the time of awakening on the day of assessment (including sleeping hours) once daily, subjects will assess the degree of itching by themselves and record the score in the symptom diary. According to Appendix 4, the symptoms during the day and the night will be assessed on a scale ranging from 0 to 4, where 0 represents no symptoms and 4 represents severe itching.

- Degree of the symptom during the day: Degree of the most severe itching during the day between the time of awakening on the previous day of assessment and the time of going to bed on the previous day of assessment
- Degree of the symptom during the night: Degree of the most severe itching during the night between the time of going to bed on the previous day and the time of awakening on the day of assessment

9.4.2 Skindex-16

At the first visit of each week (before dosing of the study drug), subjects will look back on the condition of itching in the past week and assess how often they were bothered by itching. According to Appendix 5, the frequency of itching will be assessed on a scale ranging from 0 to 6, where 0 represents never bothered and 6 represents always bothered.

9.4.3 5-D itch scale

At the first visit of each week (before dosing of the study drug), subjects will look back on the condition of itching in the past 2 weeks and assess the 5 components of itching (duration, degree, direction, disability, distribution) according to Appendix 6.

9.4.4 PGIC

At the first visit of each week, subjects will compare the overall symptom of itching with the symptom in the screening period, and assess it on a 7-level scale consisting of very much improved, much improved, minimally improved, no change, minimally worsened, much worsened, and very much worsened, according to Appendix 7.

9.5 Laboratory Tests

Blood samples will be collected for the tests listed below before the first dialysis of each week. Laboratory test values will be determined centrally at the laboratory testing facility. Only the presence or absence of collected samples will be recorded in the case report form.

9.5.1 Hematology

Red blood cell count, hemoglobin, hematocrit, white blood cell count, differential white blood cell count (neutrophil, eosinophil, basophil, monocyte, lymphocyte), platelet count

9.5.2 Blood biochemistry

AST, ALT, γ-GTP, CRP, LDH, ALP, total protein, albumin, glycoalbumin (only in subjects with concurrent diabetes mellitus), glucose, total cholesterol, total bilirubin, direct bilirubin, creatinine, BUN (before and after dialysis), Na, K, Cl, Ca, P, serum iron, UIBC, TIBC, TSAT, ferritin

9.5.3 Endocrinology

Testosterone, free testosterone, prolactin, TSH, FT3, FT4, intact-PTH, antidiuretic hormone

9.6 Vital Signs (Blood Pressure, Pulse Rate, Body Temperature)

Before the first dialysis of each week, sitting systolic blood pressure, diastolic blood pressure, and pulse rate will be measured after a period of rest. Body temperature will also be measured before dialysis. The date and result of measurement will be recorded in the case report form.

The same testing device will be used in the same subject throughout the study period in principle.

9.7 Body Weight

Before and after the first dialysis of each week, body weight will be measured. The date, timing, and result of measurement will be recorded in the case report form.

9.8 12-Lead ECG

Before the first dialysis and before blood sampling of each week, 12-lead ECGs will be obtained in the supine position after a period of rest, and the date of measurement and the presence/absence of abnormal findings will be recorded in the case report form. ECG charts will be retained at the study site.

The same testing device will be used in the same subject throughout the study period in principle.

9.9 Dependency Assessment

Using the questionnaire shown in Appendix 8, the principal investigator or subinvestigator will rate the dependency on a 4-level scale from remarkable to none.[18)]

The dependency assessment members will perform dependency assessment based on the questionnaire. Details are stipulated in a separate written procedure.

9.10 Pregnancy Test

In women of childbearing potential (those who have not undergone total hysterectomy or bilateral total ovariectomy and within 1 year of their last menstrual period), a pregnancy test (serum HCG) will be performed to determine whether the subject is pregnant or not. Pregnancy will be determined centrally at the laboratory testing facility. The presence or absence of collected samples and the presence or absence of pregnancy will be recorded in the case report form.

9.11 Pharmacokinetics

Plasma concentrations of MR13A9 (unchanged drug) will be measured. Plasma concentrations of MR13A9 will be determined using an LC-MS/MS method at the bioanalytical laboratory. The date and time of blood sampling will be recorded in the case report form. Details are stipulated in a separate study plan.

9.12 Adverse Events

An adverse event is defined as any unfavorable or unintended sign, symptom, exacerbation of a complication, or disease in a subject, whether or not considered related to the study drug. Exacerbation of any variable used for individual efficacy evaluations will not be regarded as an adverse event.

9.12.1 Collection of adverse events

Adverse event information to be recorded in the case report form will include adverse event term, date of onset, date of resolution (when the outcome of an adverse event is resolved, resolved with sequelae, or fatal), severity, seriousness assessment, action taken with study treatment and other actions taken, outcome, causal relationship with study treatment, and assessment of adverse events of special interest. For any adverse event reported between the time of signing informed consent and the start of study treatment, adverse event term, seriousness assessment, and assessment of adverse events of special interest will be recorded in the case report form.

9.12.1.1 Adverse event collection period

Adverse events will be collected between the time of signing informed consent and the final visit in the follow-up period.

9.12.1.2 History of adverse events

When interviewing each subject about his/her condition, the principal investigator or subinvestigator will pay due attention not to influence spontaneous reporting from the subject; for example, asking a general question such as “How have you been doing since the previous visit?”

9.12.1.3 Considerations for the recording of adverse events

1) Any diagnosis identified from signs and/or symptoms will be recorded as an adverse event term. The laboratory abnormality, abnormal finding, or symptom associated with the adverse event will not be regarded as the adverse event.
2) If no diagnosis can be identified from signs and/or symptoms, the laboratory abnormality, abnormal finding, or symptom will be regarded as the adverse event.

3) A laboratory abnormality or abnormal finding will be regarded as an adverse event when it is regarded as a clinically significant variation or change by the principal investigator or subinvestigator. A clinically significant variation or change is defined as a laboratory abnormality or abnormal finding that requires a medical intervention or treatment or is considered to be a variation or change that exceeds the normal range of the subject's physiological variation by the principal investigator or subinvestigator.

4) Any laboratory abnormality or abnormal finding in a test at the start of the screening period will not be regarded as an adverse event.

5) Any disease, symptom, or finding that has been present since before the informed consent procedure will not be regarded as an adverse event.

6) Any exacerbation of a complication, preexisting symptom, or finding will be regarded as an adverse event. Exacerbation of a complication, preexisting symptom, or finding is defined as an exacerbation of a disease, symptom, or finding present before study participation considered to be greater than expected by the principal investigator or subinvestigator, or an increased frequency or an increased seriousness or severity of a seasonal or intermittent symptom or finding.

7) Any exacerbation after the start of study treatment of an adverse event that has occurred between the time of signing informed consent and the start of study treatment will be regarded as a new adverse event.

8) Any operation or treatment scheduled before the time of signing informed consent will not be regarded as an adverse event.

9) Any elective operation or treatment that will not alter the disease condition (e.g., dental implant, cosmetic surgery, or suture removal after skin suture at the request of the subject) will not be regarded as an adverse event. However, if any of these interventions causes a clinically significant finding or symptom, the event will be regarded as an adverse event.

9.12.2 Date of onset of adverse events

- Day when the subject, principal investigator or subinvestigator becomes aware of the sign or symptom of an adverse event
- Day when the subject, principal investigator or subinvestigator becomes aware of the exacerbation of a complication, preexisting symptom, or finding
- Day of confirmed diagnosis of an asymptomatic disease, of which time of onset can be estimated
- Day of a test that yields a laboratory abnormality or abnormal finding considered to be a clinically significant variation or change by the principal investigator or subinvestigator

9.12.3 Severity of adverse events

The severity of adverse events will be categorized into 3 grades according to Table 9.12.3-1. For an adverse event in which the severity changes, the highest severity will be recorded.

Table 9.12.3-1 Severity of adverse events

Severity	Criteria
Mild	Not or minimally interfering with daily activities[a)] and requiring no special treatment or simple treatment

Moderate	Somewhat interfering with daily activities[a)] and requiring treatment
Severe	Largely interfering with daily activities[a)] or requiring systemic treatment

a) Include sleeping, movements, work, going out, eating, exercise, bathing

9.12.4 Serious adverse events

All adverse events, including those occurring between the time of signing informed consent and the start of study treatment, that meet any of the following criteria will be regarded as serious adverse events. For any serious adverse event, its symptom or laboratory test and the reason for assessing it as serious will be recorded in the case report form.

1) Results in death
2) Is life-threatening
3) Requires inpatient hospitalization or prolongation of existing hospitalization
4) Results in persistent or significant disability/incapacity
5) Is a congenital anomaly/birth defect
6) Is a serious condition corresponding to 1) to 5) above

A serious condition corresponding to 1) to 5) above refers to any important medical event that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention or treatment to prevent the outcomes listed in the definitions 1) to 5) above.

9.12.5 Adverse events of special interest

On the day of the first dialysis of each week, the principal investigator or subinvestigator will ask each subject about specific signs or symptoms occurring in the past week and record them, referring to Appendix 2. Any specific sign or symptom corresponding to an adverse event will be recorded as an adverse event of special interest (of any seriousness). Details are stipulated in a separate procedure.

- Considerations for the recording of adverse events of special interest

1) Any new sign or symptom (i.e., never occurred before or not included in the subject's medical history) will be recorded as an adverse event in the case report form.
2) Any sign or symptom already present within 3 months prior to the start of the screening period (i.e., included in the subject's medical history) will be recorded as an adverse event in the case report form only when its severity or frequency has increased compared with baseline.
3) For any sign or symptom that is part of a definitive diagnosis, the diagnosis will be recorded as an adverse event.
4) Any sign or symptom that does not meet the criteria 1) or 2) above will not be recorded as an adverse event.

9.12.6 Action taken with study treatment

Actions taken with study treatment are defined in Table 9.12.6-1.

Table 9.12.6-1 Action taken with study treatment

Action	Definition
Drug withdrawn	Study treatment is discontinued due to the adverse event, including at the subject's request.
Dose not changed	No action is taken and study treatment is continued.
Unknown	Action taken with study treatment is unknown.
Not applicable	Study treatment is already completed or discontinued for reasons other than the adverse event at the time when the adverse event occurred
Drug Interrupted	Study treatment is interrupted due to the adverse event, including at the subject's request.

9.12.7 Outcome of adverse events

The outcome of each adverse event will be assessed according to Table 9.12.7-1.

Table 9.12.7-1 Outcome of adverse events

Outcome	Criteria
Recovered/Resolved	The symptom has disappeared or resolved. The test value has returned to normal or baseline level.
Recovering/Resolving	The severity of the symptom/abnormal value has reduced or has been improving.
Not recovered/Not resolved	The symptom/abnormal value has changed little or worsened.
Recovered/Resolved with sequelae	The symptom/abnormal value has caused dysfunction that interferes with daily activities.
Fatal	The symptom/abnormal value has caused death. * This category will not be selected if the subject's death is not related to the symptom/abnormal value.
Unknown	Confirmation of outcome is impossible despite efforts to follow-up the symptom/abnormal value.

9.12.8 Causal relationship between adverse events and study treatment

Based on the subject's condition, complications, past history, concomitant medications, and temporal relationship with time to onset, the causal relationship between an adverse event and study treatment will be classified into 2 categories according to Table 9.12.8-1. Any adverse event occurring after the start of study treatment of which causal relationship with study treatment is assessed as related will be regarded as an adverse drug reaction.

The causal relationship between any adverse event occurring secondary to another adverse event and study treatment will be assessed separately.

Table 9.12.8-1 Causal relationship between adverse events and study treatment

Causality	Criteria
Related	The adverse event is believed to be related to study treatment because the onset of the adverse event can be explained easily from the subject's condition, complications, past history, concomitant medications, and the temporal relationship with time to onset
Not related	The adverse event that does not fall into the above criterion of the presence of causal relationship with the study drug, specifically when the event falls into one of the following criterion: • It is clear that the adverse event is attributable to factors other than study treatment. • No temporal correlation or a discrepancy is found between the onset/resolution of the adverse event and study treatment. • The onset of the adverse event is considered to be incidental (e.g., the same event was observed repeatedly before the study, and the adverse event occurring during the study is also considered to be in the same range). • The adverse event is attributable to factors other than study treatment, such as the

	subject's medical history or condition, concomitant medications or therapies, and diet.

9.12.9 Follow-up investigation

The principal investigator or subinvestigator will follow up any serious adverse event occurring between the informed consent procedure and the start of study treatment or adverse event occurring after the start of study treatment, when considering that its symptom (including test values) has not recovered to the state before its onset or resolved, until either of the time points below:

1) When the principal investigator or subinvestigator deems that the event has recovered or resolved
2) When the principal investigator or subinvestigator deems further follow-up investigation as unnecessary

10. Investigations, Observations, Tests, and Evaluations at Each Time Point

The principal investigator, subinvestigator, and clinical research coordinator will perform investigations, observations, tests, and evaluations according to the study schedule and their respective procedures. Tests and evaluations will be performed on the day of the first dialysis of each week, unless prescribed otherwise.

10.1 At the Time of Signing Informed Consent

- Confirmation of written informed consent
- Confirmation of subject demographics

10.2 At Week −2

- Confirmation of subject demographics
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Confirmation of the implementation status of hemodialysis
- Body weight (before and after dialysis)
- 12-lead ECG
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology, postdialysis BUN)
- Pregnancy test (only in women of childbearing potential)
- Confirmation of eligibility and subject registration
- Instructions for the symptom diary

10.3 At Week −1

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Examination of specific signs and symptoms

- Confirmation of the implementation status of hemodialysis

10.4 At Week 0

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Examination of specific signs and symptoms
- Confirmation of the implementation status of hemodialysis
- Skindex-16
- 5-D itch scale
- Body weight (before dialysis)
- 12-lead ECG
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of eligibility and subject registration
- Confirmation of the compliance with study treatment

10.5 At Week 1

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Examination of specific signs and symptoms
- Confirmation of the implementation status of hemodialysis
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment
- Pharmacokinetics (before the first dialysis and at 5 minutes after administration of the week, before the second dialysis)

10.6 At Week 2

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Examination of specific signs and symptoms
- Confirmation of the implementation status of hemodialysis
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment
- Pharmacokinetics (before the first dialysis of the week)

10.7 At Week 3

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Examination of specific signs and symptoms
- Confirmation of the implementation status of hemodialysis

10.8 At Week 4

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Examination of specific signs and symptoms
- Confirmation of the implementation status of hemodialysis
- Skindex-16
- 5-D itch scale
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment
- Pharmacokinetics (before the first dialysis and at 5 minutes after administration of the week, before the second dialysis)

10.9 At Weeks 5 and 6

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Examination of specific signs and symptoms
- Confirmation of the implementation status of hemodialysis

10.10 At Week 7

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Examination of specific signs and symptoms
- Confirmation of the implementation status of hemodialysis
- Confirmation of the compliance with study treatment
- Pharmacokinetics (before the first dialysis, and at 5 minutes and at least 1 hour* after administration of the week, before the second dialysis)

*: To be performed only in subjects from whom blood can be collected.

10.11 At Week 8 or at the Time of Discontinuation

- Review of the symptom diary

- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Examination of specific signs and symptoms
- Dependency assessment (before the first dialysis of Week 8 or before dialysis on the day of the assessments at discontinuation)
- Confirmation of the implementation status of hemodialysis
- Skindex-16
- 5-D itch scale
- PGIC
- Body weight (before dialysis)
- 12-lead ECG
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Pregnancy test (only in women of childbearing potential)
- Pharmacokinetics (before the first dialysis of Week 8 or before dialysis on the day of the assessments at discontinuation)

10.12 At Week 9 (Week 1 of the Follow-up Period) or Week 1 after Discontinuation

Assessments at Week 1 after discontinuation will be performed on the same day of the week for the assessments at discontinuation.

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Examination of specific signs and symptoms
- Dependency assessment (before the first dialysis of Week 9 or before dialysis at Week 1 after discontinuation)
- Confirmation of the implementation status of hemodialysis

10.13 At Week 10 (Week 2 of the Follow-up Period) or Week 2 after Discontinuation

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Confirmation of the implementation status of hemodialysis
- Examination of specific signs and symptoms
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)

11. Measures to Ensure the Safety of the Clinical Study

11.1 Action to be Taken for Adverse Events

If any adverse event occurs in a subject during the study period, the principal investigator or subinvestigator will take appropriate action to ensure the safety of the subject. Any adverse event that meets the criteria described in "9.12.9 Follow-up investigation" will be followed up, as instructed in the section.

11.2 Action to be Taken for and Response to Serious Adverse Events

11.2.1 Action to be taken for serious adverse events

If any serious adverse event described in "9.12.4 Serious adverse events" occurs in a subject, the principal investigator or subinvestigator will make efforts to provide the subject with appropriate emergency treatment for recovery.

11.2.2 Response to serious adverse events

The principal investigator or subinvestigator will inform the monitor of a serious adverse event within 24 hours of knowledge of its occurrence, and the principal investigator will submit a prespecified document within 3 days of knowledge of the occurrence.

In addition, the principal investigator will immediately report the event to the head of the study site, as instructed by the study site's procedure.

11.3 Action to be Taken for and Response to Pregnancies

If a female subject is found or suspected to be pregnant during the study period, the principal investigator or subinvestigator will immediately discontinue study treatment in the subject. If obtained any information about a suspected pregnancy, the principal investigator or subinvestigator will immediately provide the sponsor with the information. In addition, the principal investigator or subinvestigator will follow up the course from pregnancy until delivery as well as the postnatal development of her baby for about one and half years, and provide obtained information for the sponsor. However, it is unnecessary to follow up the subject if she is found to have been in the placebo group after unblinding.

If obtained information about a pregnancy or suspected pregnancy of the partner of a male subject during the period between the start of study treatment and 12 weeks after the day of the final dose, the principal investigator or subinvestigator will immediately provide the sponsor with the information. In addition, the principal investigator or subinvestigator will follow up the course of the partner's pregnancy whenever possible and provide obtained information for the sponsor.

11.4 Collection and Provision of Safety Information

11.4.1 Collection of new safety information

The sponsor will continuously collect and assess information that may adversely affect the safety of subjects, influence the conduct of the clinical study, or require changes to the approval of the IRB for continuation of the study.

11.4.2 Provision of new safety information

The sponsor will promptly notify all the principal investigators involved in the study, the head of the study site, and the IRB via the head of the study site in writing of any new information on the safety of the investigational product that is considered necessary to be reported to the principal investigator or subinvestigator. If any agreement has been made in advance among the sponsor, the IRB, and the head of the study site, the sponsor may also notify the IRB at one time of only notifications concerning Article 20, Paragraphs 2 and 3 of the GCP ordinance.

When considering that any information may affect the subject's willingness to continue participation in the study, the principal investigator or subinvestigator will immediately notify the subject of the information and reconfirm the subject's willingness to continue participation in the study. At this time, the communication of the information to the subject and the result of reconfirmation of the subject's willingness to continue participation in the study will be documented in writing (such as in medical records). In addition, when considering it necessary to revise the informed consent form, the principal investigator will promptly revise the informed consent form on the basis of the information and obtain approval of the IRB in advance. For subjects already participating in the study, the principal investigator or subinvestigator will provide an explanation about details again using the revised informed consent form and obtain voluntary consent in writing for continuation of participation in the study from the subjects. In principle, new subjects will not be enrolled in the study until the revised informed consent form is approved. However, enrollment will be permitted when the sponsor or the principal investigator consider it unnecessary to change, terminate, or suspend the study. In this case, the informed consent form before revision will be used, and any new safety information that may affect the subject's willingness to continue participation in the study will be conveyed and documented. After given approval by the IRB, reconsent will be obtained using the revised informed consent form.

12. Discontinuation/Suspension of the Clinical Study

12.1 Discontinuation/Suspension of Parts of the Study or the Entire Study

If any of the following discontinuation criteria are met during the study, the sponsor or the principal investigator will determine measures to be taken, taking into consideration discontinuation/suspension of parts of the study or the entire study.

12.2 Discontinuation Criteria (Discontinuation/Suspension of Parts of the Study or the Entire Study)

1) It is considered difficult to continue the study because of new safety information (including the occurrence of a serious adverse event).
2) It is considered difficult to properly continue the study because of a serious violation of GCP, the protocol, or the agreement by the sponsor, study site, or principal investigator.
3) It is considered difficult to continue the study because of a change in the study administrative structure (e.g., transfer of the principal investigator).
4) It is considered inappropriate to continue the study for other reasons such as new information or a change in circumstances during the study.

12.3 Procedures for Discontinuation/Suspension

The study will be discontinued or suspended in the following procedures:

1) When the sponsor discontinues/suspends parts of the study or the entire study, the sponsor will immediately notify the head of the study site in writing of the decision on discontinuation/suspension and the reason for the decision.

2) When the principal investigator discontinues/suspends the study, the principal investigator will immediately notify the head of the study site in writing of the decision on discontinuation/suspension and the reason for the decision.

3) When the sponsor decides to discontinue/suspend parts of the study or the entire study and notifies the head of the study site of the decision, the head of the study site will immediately notify the principal investigator and the IRB in writing of the decision and the reason for the decision. When the principal investigator discontinues/suspends the study and notifies the head of the study site of the decision, the head of the study site will immediately notify the sponsor and the IRB in writing of the decision and the reason for the decision.

When receiving the notice of discontinuation/suspension of the study, the principal investigator will immediately convey the notice to subjects on treatment and take appropriate action for them.

13. Statistical Analysis

Data will be analyzed by the person in charge of statistical analysis as instructed by the statistical analysis manager. Major analysis methods are described below, and details of the statistical analyses will be defined in a statistical analysis plan prepared separately before the database lock. Any necessary analysis other than the prespecified analyses will be performed using an appropriate method at the discretion of the statistical analysis manager.

Handling of subjects and data will be determined before the database lock.

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 the number of subjects, mean, standard deviation, minimum, median, maximum, and quartile. Data will be tabulated by group and by time point, unless otherwise specified.

13.1 Analysis Sets

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 assigned. 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 treated actually.

- 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

13.2 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

13.3 Disposition of Subjects

For the each analysis set and the presence/absence of discontinuation, numbers and percentages of subjects will be presented and the imbalance between the groups will be examined.

13.4 Demographic and Other Baseline Characteristics

For major subject demographics, summary statistics or numbers and percentages of subjects will be presented overall and by group according to the characteristics of individual data, and imbalance between the groups will be examined.

13.5 Efficacy

The FAS will be used as the primary analysis set. As a supplementary analysis, the PPS will be used for the primary analysis of the primary variable to determine the robustness of the analysis results.

13.5.1 Primary endpoint

The primary endpoint is the NRS score. The assessment time points and their evaluated time windows in the treatment period and the follow-up period are shown in Table 13.5.1-1 and Table 13.5.1-2, respectively.

Table 13.5.1-1 Assessment time points and evaluated time windows in the treatment period

Time point	Evaluated time window[a)]
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 13.5.1-2 Assessment time points and evaluated time windows in the follow-up period

Time point	Evaluated time window[a)]
Week 1	From Day 1 to Day 7
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

13.5.2 Primary variable

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

13.5.2.1 Analysis of the primary variable

13.5.2.1.1 Primary analysis

The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with 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, presence of prior treatment with nalfurafine hydrochloride, and 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 adjusted mean change at each time point for each group and its two-sided 95% confidence interval will be presented. The adjusted mean between-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.

13.5.2.1.2 Sensitivity analysis

The sensitivity analyses shown below will be performed to determine the robustness of the analysis results. Details of the multiple imputation (MI) method are described separately in the statistical analysis plan.

In the individual sensitivity analyses, as with the primary analysis, contrasts will be used to determine dose-response relationships and estimate treatment effects.

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.

13.5.2.2 Other assessment variables

1) Mean NRS score

For changes from baseline, 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.

For the mean NRS score, summary statistics will be presented.

13.5.3 Secondary endpoints

1) Itch score based on the Shiratori's severity criteria

The mean itch score and 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 "13.5.1 Primary endpoint."

For changes from baseline, 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.

For mean itch scores, summary statistics will be presented.

2) Total Skindex-16 score and total 5-D itch scale score

For changes from baseline, 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.

For measurements, summary statistics will be presented.

3) 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.

13.6 Safety

The SS will be used as the analysis set.

13.6.1 Adverse events and adverse drug reactions

Analysis will include events occurring between the start of study treatment and the end of the follow-up period. Analysis of adverse drug reactions will be similar to adverse events.

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 between-group difference in the incidence of events and its two-sided 95% confidence interval will be presented.

2) Incidences of adverse events and adverse drug reactions (serious events and events led to discontinuation)

The numbers of events, the numbers of subjects experiencing events, and the incidences of events will be presented for all events, events led to death, serious events other than death, and events led to discontinuation.

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.

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.

13.6.2 Vital signs and body weight

Summary statistics will be presented. Scatterplots before and after treatment will be presented.

13.6.3 Laboratory tests

For quantitative values, summary statistics will be presented. Scatterplots before and after treatment will be presented. Shift tables before and after treatment will be presented.

For qualitative values, the number and percentage of subjects will be presented. Shift tables before and after treatment will be presented.

13.6.4 Dependency assessment

The number and percentage of subjects with or without dependency will be presented.

13.7 Pharmacokinetics

The PKS will be used as the analysis set.

13.7.1 Plasma drug concentration

For plasma concentrations of MR13A9 (unchanged drug), summary statistics, geometric means, and geometric CVs will be presented. Geometric means and individual values will be illustrated by dose group.

14. Protocol Agreement and Amendment

14.1 Agreement on the Protocol

To confirm the agreement on the content of the protocol and the compliance with the protocol, the principal investigator and the sponsor will affix their name and seal to or sign, and date the protocol or an alternative document.

14.2 Amendment of the Protocol

The sponsor will revise the protocol as necessary when becoming aware of information on the quality, efficacy, and safety of the test drug and other important information for the proper conduct of the study. In such cases and in cases where the protocol is revised on the order of the head of the study site based on IRB's opinion, the sponsor will agree with the principal investigator on the revision of the protocol.

The principal investigator or subinvestigator must not implement any deviation from or changes of the protocol unless the principal investigator obtains prior written agreement from the sponsor and written approval from the IRB based on its prior review, except where medically necessary to eliminate immediate hazards to subjects, or when the change involves only administrative aspects of the study.

14.3 Deviation from the Protocol

When having implemented a deviation from or a change to the protocol to eliminate immediate hazards to subjects or for other inevitable medical reasons, the principal investigator will submit a document describing the deviation or change and the reason for it, as well as a proposed protocol revision when protocol revision is necessary, as soon as possible, to the sponsor, the head of the study site, and the IRB via the head of the study site. By doing so, the principal investigator will obtain approval from the head of the study site and written agreement from the sponsor via the head of the study site. The principal investigator or subinvestigator will document all deviations from the protocol.

15. Direct Access to Source Documents

15.1 Source Documents

Source documents refer to original documents, data, and records that contain source

information for case report forms. More specifically, source documents refer to records, such as informed consent forms, subject's medical records, laboratory data, and study treatment records, necessary for the reconstruction and evaluation of the course of events in the study. In addition, the study site will consult with the sponsor and specify source documents.

15.2 Direct Access

The head of the study site and the principal investigator must allow monitoring and auditing by the sponsor and inspections by the IRB and regulatory authorities in and outside Japan, providing direct access to source documents.

The sponsor will confirm that each subject has consented in writing to direct access to their original medical records at the time of monitoring, auditing, and inspections by the IRB and regulatory authorities in and outside Japan.

15.3 Consistency Between Source Documents and Case Report Forms

The sponsor will confirm that the entries in case report forms completed by the principal investigator and study-related records such as source documents are accurate by checking them against each other.

The entries in case report forms must be consistent with the contents in source documents. The principal investigator will prepare a record explaining the reason for any discrepancy between case report forms and source documents and submit the record to the sponsor. A copy of the record will be retained at the study site.

16. Quality Control and Quality Assurance for the Study

The sponsor will implement quality control and quality assurance for this study according to the standard operating procedures. The sponsor's auditor will assess whether this study is being conducted in compliance with GCP, protocol, and written procedures, independently and separately from the routine monitoring and study quality control activities.

17. Ethics

17.1 Compliance with GCP

This study will be conducted in accordance with the ethical principles that have their origin in the latest Declaration of Helsinki and in compliance with Article 14-3 and Article 80-2 of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, the standards related to the conduct of clinical studies of drugs stipulated by the Ministry of Health, Labour and Welfare, the MHLW Ordinance on Good Clinical Practice, and this protocol.

17.2 Protection of Subject Confidentiality

The head of the study site will take necessary measures to guarantee the protection of subject confidentiality. Sufficient care for the protection of human rights will be taken, including identification of subjects by subject identifiers in documentation of subject data in the case report form. In addition, measures will be taken to ensure that subject confidentiality is protected when the monitors, auditors, IRB, and regulatory authorities access the subjects'

source data.

17.3 Compensation to Subjects

1) The study site will provide treatment or other necessary measures for a subject experiencing any study-related injury.
2) If a subject makes or may make a claim for compensation or indemnification from the study site for a study-related injury, the study site will immediately notify the sponsor, and the study site and the sponsor will cooperate to settle the issue.
3) The sponsor will compensate a subject experiencing any study-related injury in accordance with the compensation rules specified by the sponsor.
4) If responsibilities arise later for damage from a study-related injury to a subject in this study, the compensation will be the responsibility of and at the expense of the party liable for the damage.
5) The sponsor will insure against the compensation or indemnification mentioned above.

18. Data Handling, and Record Keeping

18.1 Preparation and Submission of Case Report Forms

In this study, clinical study data on investigations, observations, tests, and evaluations will be collected and recorded electronically to complete case report forms. The principal investigator or subinvestigator will complete case report forms for all subjects who have provided informed consent, and the principal investigator will review all entered data. For subjects not entering into the treatment period, only the information on the date of written informed consent, the information on the investigations, observations, tests, and evaluations performed at Week −2, adverse events, concomitant medications, concomitant therapies, implementation status of dialysis, and the information on the discontinuation of the study will be collected and recorded. Case report forms will be completed as instructed separately in the written procedure.

18.2 Recording of the Symptom Diary

Subjects will record their symptoms in the symptom diary based on the electronic diary system. Data recorded by subjects will be transferred to electronic case report forms, and the case report forms will be regarded as source documents. The contents of the case report forms will be checked by the principal investigator, subinvestigator, or clinical research coordinator during interviews and when necessary. Record forms prepared at the time of electronic diary system troubles will be checked by the principal investigator or subinvestigator during interviews. These record forms will be retained at the study site. The symptom diary will be recorded and amended as instructed separately in the written procedure.

18.3 Preparation and Submission of Forms for 12-Lead ECG Charts

If any abnormal finding corresponding to an adverse event is observed in a subject after administration of the study drug and the sponsor considers it necessary to do so, the principal investigator or subinvestigator will attach copies of all ECG charts for the subject obtained during the study to a 12-lead ECG chart form, and submit the form to the sponsor.

The principal investigator, subinvestigator, or clinical research coordinator will attach copies

of 12-lead ECG charts to a 12-lead ECG chart form, and enter the subject identification code and the time of measurement in the form. The principal investigator or subinvestigator will check all the entries, enter the date of confirmation and sign (or affix the name and seal to) the form, and submit the form to the sponsor.

18.4 External Data

For measurements at an external laboratory testing facility, the sponsor will obtain their electronic data directly from the external laboratory testing facility. The method and time of data generation will be in accordance with a procedure established between the sponsor and the external laboratory testing facility.

18.5 Record Keeping

18.5.1 Study site

The head of the study site will retain study-related documents and records until notified by the sponsor that the retention of study-related documents and records is no longer necessary. The head of the study site or the record retention manager will take measures to prevent the loss or disposal of these records during a time period of retention and to make these records available upon request.

The principal investigator will retain study-related documents, as instructed by the head of the study site.

18.5.2 Institutional review board

The founder of the IRB will retain study-related documents and records until notified by the sponsor that the retention of study-related documents and records is no longer necessary. These records must be made available upon request from the regulatory authorities.

18.5.3 Notice from the sponsor

When the retention of study-related documents and records by the head of the study site or the founder of the IRB is no longer needed, the sponsor will notify the head of the study site and the founder of the IRB via the head of the study site.

19. Monetary Payment

The study site and the sponsor will discuss any monetary payment to a subject in advance and obtain approval of the IRB. If the IRB's approval is obtained, money should be paid to the subject based on the documented rules for payment to subjects.

20. Publication Policy

Information, including unpublished data included in this protocol, is the property of the sponsor and may not be disclosed to any third party without written consent of the sponsor. Disclosure of the results of the study to outside parties such as academic societies or journals, in part or in whole, will require the prior approval of the sponsor.

21. Study Administrative Structure

This study will be planned and conducted by the organizations shown in the attachment. Any

amendment of the attachment will be managed separately from the protocol.

22. History of Protocol Amendments

Version 02.00.000: created on November 29, 2018

23. Literature References

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Study Schedule

	Screening period			Treatment period																					Follow-up period						
Visit[a] (weeks after initial dose)		Week −2	Week −1	Week 0			Week 1			Week 2			Week 3			Week 4			Week 5–6			Week 7			Week 8			Week 9			Week 10
Visit	—	1	—	2	—	—	3	4	—	5	—	—	—	—	—	6	7	—	—	—	—	8	9	—	10	—	—	11	—	—	12
Day of the week	—	Mon /Tue	Mon /Tue	Mon /Tue	Wed /Thu	Fri /Sat	Mon /Tue	Wed /Thu	Fri /Sat	Mon /Tue	Wed /Thu	Fri /Sat	Mon /Tue	Wed /Thu	Fri /Sat	Mon /Tue	Wed /Thu	Fri /Sat	Mon /Tue	Wed /Thu	Fri /Sat	Mon /Tue	Wed /Thu	Fri /Sat	Mon /Tue	Wed /Thu	Fri /Sat	Mon /Tue	Wed /Thu	Fri /Sat	Mon /Tue
Informed consent[b]	●																														
Eligibility assessment	●	●		●																											
Subject demographics	●	●																													
Subject registration	Primary	Secondary		Tertiary																											
Study treatment				●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●							
NRS[c] Shiratori's severity criteria[c]																															
Adverse events Concomitant medications/therapies																															
Specific signs/symptoms[d]			●	●			●			●			●			●			●			●			●			●			●
Prohibited concomitant medications Hemodialysis conditions																															
Skindex-16 5-D itch scale				●												●									●						
PGIC																									●						
Body weight[e] 12-lead ECG[e]		●		●																					●						
Vital signs[e] Laboratory tests[e]		●		●			●			●						●									●						●
Postdialysis BUN Postdialysis weight		●																													
Dependency assessment[f]																									●			●			
Serum pregnancy test[g]		●																							●						
Pharmacokinetics[h]							●	●		●						●	●					●	●		●						

a) Assessments and tests will be performed on the day of the first dialysis of each week, unless prescribed otherwise.
b) Consent for study participation must be obtained prior to the start of the screening period.
c) To be recorded in the symptom diary once daily from the next day of the start date of the screening period until the visit day at Week 10.
d) Subjects will be examined for specific signs/symptoms every week (Monday or Tuesday) from Week −1 until Week 10.
e) To be performed before dialysis.
f) To be performed before dialysis at Week 8.
g) To be performed only in women of childbearing potential (within 1 year of their last menstrual period and who have not undergone total hysterectomy or bilateral total ovariectomy).
h) Blood samples will be collected at Week 1 (before the first dialysis, at 5 minutes after administration of the week, before the second dialysis), Week 2 (before the first dialysis of the week), Week 4 (before the first dialysis, at 5 minutes after administration of the week, before the second dialysis), Week 7 (before the first dialysis, at 5 minutes and of the week, at least 1 hour after administration, before the second dialysis), and Week 8 (before the first dialysis of the week). At least 1 hour after administration at Week 7, blood sampling will be performed only in subjects from whom blood can be collected.

Study Schedule (at the time of discontinuation)

	Treatment period	Follow-up period			
Visit (weeks after initial dose)	**At discontinuation** [a]	**Week 1 after discontinuation**	**Week 2 after discontinuation**		
Visit	—	—	—		
Day of the week	—	—[b]	Mon /Tue	Wed /Thu	Fri /Sat
Study treatment					
NRS[c] Shiratori's severity criteria[c]	→	→	→		
Adverse events Concomitant medications/therapies	→	→	→		
Specific signs/symptoms[d]	●	●	●		
Prohibited concomitant medications Hemodialysis conditions	→	→	→		
Skindex-16 5-D itch scale	●				
PGIC	●				
Body weight[e] 12-lead ECG[e]	●				
Vital signs[e] Laboratory tests[e]	●		●		
Postdialysis BUN Postdialysis weight					
Dependency assessment	●[e]	●			
Serum pregnancy test[f]	●				
Pharmacokinetics[e]	●				

a) Assessments and tests will be performed on the day of dialysis after discontinuation has been decided.
b) Assessments at Week 1 after discontinuation will be performed on the same day of the week as the day of the assessments at discontinuation.
c) To be recorded in the symptom diary once daily from the next day of the start date of the screening period until the visit day at Week 2 after discontinuation.
d) Subjects will be examined for specific signs/symptoms at the time of discontinuation, at Week 1 after discontinuation, and at Week 2 after discontinuation.
e) To be performed before dialysis.
f) To be performed only in women of childbearing potential (within 1 year of their last menstrual period and who have not undergone total hysterectomy or bilateral total ovariectomy).
* Subjects discontinuing the study in the treatment period will undergo the assessments at discontinuation and enter into the follow-up period.

24. Appendices

Appendix 1 New York Heart Association (NYHA) Classification

Class I: Patients with cardiac disease but without resulting in limitation of physical activity.

- Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest.

- Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest.

- Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

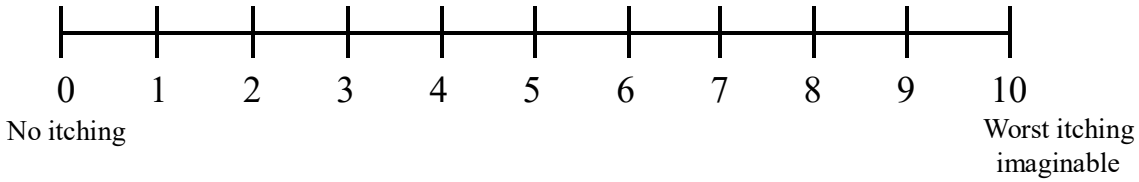
Class IV: Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort.

- Symptoms of heart failure or the anginal pain may be present even at rest. If any physical activity is undertaken, discomfort increases.

Appendix 2 Specific signs or symptoms

1) Dizziness (e.g., lightheadedness, vertigo)
2) Syncope (e.g., fainting spells)
3) Palpitation (e.g., heart pounding)
4) Tachycardia (as per vital sign assessment)
5) Falls (including fractures due to falls)
6) Seizures (including convulsions)
7) Gait disturbance (e.g., unsteady gait, unsteady on feet while walking)
8) Mental status change (e.g., patient appears confused, spatially or temporally disoriented, forgetful)
9) Somnolence (e.g., patient appears sleepier, drowsy, sedated, groggy)
10) Mood changes (e.g., patient appears more anxious, agitated, aggressive, uncooperative, restless, withdrawn)

Appendix 3 Numerical Rating Scale (NRS)



Appendix 4 Shiratori's severity criteria

Severity	Daytime symptom	Nighttime symptom
4: Severe itching	Intolerable itch, not relieved by scratching but instead worsens. Cannot focus on work or study.	Can hardly sleep because of itch. Scratching all the time, but itch intensifies with scratching.
3: Moderate itching	Scratching even in the presence of others. Irritation as a result of itch, continuous scratching.	Wake up because of itch. Can fall asleep again after scratching, but continue to scratch unconsciously while sleeping.
2: Mild itching	Itch sensation is relieved by light, occasional scratching. Not too disturbing.	Feel somewhat itchy, but can obtain relief by scratching. Do not wake up because of itch sensations.
1: Slight itching	Feel itchy sometimes, but tolerable without scratching.	Feel slightly itchy when going to sleep, but do not need to scratch. Sleeping well.
0: No symptom	Hardly feel itchy or do not feel itchy at all.	Hardly feel itchy or do not feel itchy at all.

Source: Shiratori A, et al., Clinical Evaluation of Oxatomide for Pruritus–Multicenter, Double-blind Study–, Nishinihon Journal of Dermatology 1983;45:1042-51.

Appendix 5 Skindex-16

During the past 1 week, how often have you been bothered by the following?

1. Skin itching
2. Skin burning or stinging
3. Skin hurting
4. Skin irritated
5. Persistence or recurrence of condition
6. Worry about condition (e.g., that it will get worse)
7. Appearance of skin
8. Frustration about skin
9. Embarrassment about skin
10. Annoyed about skin
11. Feeling depressed
12. Effect of skin on interaction with others (e.g., family members, friends, familiar people)
13. Effect of skin in desire to be with people
14. Skin making it hard to show affection
15. Effect of skin on daily activities
16. Skin making it hard to work/have enjoyment

No. 1 to 4 is categorized into questions concerning symptoms, No. 5 to 11 are categorized into questions concerning emotions, and No. 12 to 16 is categorized into questions concerning functioning. Patients choose 1 answer to each question from among 7 scales, where 0 indicates never bothered and 6 indicates always bothered.

Appendix 6 5-D itch scale

1. Duration
During the past 2 weeks, how many hours a day have you been itching?
(1) Less than 6 hours/day, (2) 6-12 hours/day, (3) 12-18 hours/day, (4) 18-23 hours/day, (5) All day

2. Degree
Rate the intensity of your itching over the past 2 weeks.
(1) Not present, (2) Mild, (3) Moderate, (4) Severe, (5) Unbearable

3. Direction
Over the past 2 weeks, has your itching gotten better or worse compared to the previous month?
(1) Completely resolved, (2) Much better, but still present, (3) Little bit better, but still present, (4) Unchanged, (5) Getting worse

4. Disability
Rate the impact of your itching on the following activities over the past 2 weeks.
- Sleep

(1) Never affects sleep, (2) Occasionally delays falling asleep, (3) Frequently delays falling asleep, (4) Delays falling asleep and occasionally wakes me up at night, (5) Delays falling asleep and frequently wakes me up at night
- Leisure/Social

(1) Never affects this activity, (2) Rarely affects this activity, (3) Occasionally affects this activity, (4) Frequently affects this activity, (5) Always affects this activity, (*) Not applicable
- Housework/Errands

(1) Never affects this activity, (2) Rarely affects this activity, (3) Occasionally affects this activity, (4) Frequently affects this activity, (5) Always affects this activity, (*) Not applicable
- Work/School

(1) Never affects this activity, (2) Rarely affects this activity, (3) Occasionally affects this activity, (4) Frequently affects this activity, (5) Always affects this activity, (*) Not applicable

5. Distribution
Mark whether itching has been present in the following parts of your body over the past 2 weeks. If a body part is not listed, choose the one that is closest.
Head/Scalp ( ), Face ( ), Chest ( ), Abdomen ( ), Back ( ), Buttocks ( ), Thighs ( ), Lower legs ( ), Tops of feet/Toes ( ), Soles ( ), Palms ( ), Tops of hands/Fingers ( ), Forearms (below the elbow) ( ), Upper arms (from the elbow to the shoulder) ( ), Points of contact with clothing (e.g., waistband, undergarment) ( ), Groin ( )

Source: Ebata T, et al., Development of the Japanese Version of the 5-D itch scale, Japanese Journal of Dermatology 2015;125,1035-40.

Appendix 7 Patient Global Impression of Change (PGIC)

1) Very much improved
2) Much improved
3) Minimally improved
4) No change
5) Minimally worse
6) Much worse
7) Very much worse

Appendix 8 Dependency assessment

Questionnaire on the study drug (before dialysis at Week 8 or at the time of discontinuation)

Question	Remarkable	Moderate	Slight	None	Remarks Specify reason for Remarkable and Moderate
Do you feel clearheaded when using the study drug?					
Do you feel indifferent to disliked persons or things when using the study drug?					
Do you become hyperactive or talkative when using the study drug?					
Do you become broad-minded when using the study drug?					
Do you feel intoxicated when using the study drug?					
Do you feel irritable or somewhat lonely when the effect of the study drug runs out?					
Do you want to continue using the study drug?					☐ To relieve pruritus ☐ To improve mood
Do you think this drug has become less effective?					
Do you want to use the study drug in larger doses?					☐ To relieve pruritus ☐ To improve mood
Do you feel nauseated or tremulous when the effect of the study drug runs out?					

Adapted from Literature Reference 18)

Questionnaire on the study drug (at Week 9 or at Week 1 after discontinuation)

Question	Remarkable	Moderate	Slight	None	Remarks Specify reason for Remarkable and Moderate
Did you feel irritable or unstable after you discontinued the study drug?					
Did you have more difficulty in sleeping after you discontinued the study drug?					
Did you have nausea, vomiting, tremors of limb or perspiration after you discontinued the study drug?					
Do you really want to use the study drug?					☐ To relieve pruritus ☐ To improve mood
Did you have convulsions after you discontinued the study drug?					
Did you have a clouded mind or heard or seen anything unusual after you discontinued the study drug?					

Adapted from Literature Reference 18)

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