CLINICAL STUDY PROTOCOL

Title of Study:	A phase III clinical study of MR13A9 in previously treated hemodialysis patients with pruritus
Protocol No.:	MR13A9-5
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Sponsor:	Kissei Pharmaceutical Co., Ltd. [redacted]

Protocol Synopsis

Title of Study:
A phase III clinical study of MR13A9 in previously treated hemodialysis patients with pruritus
(Protocol No.: MR13A9-5)

Development Phase:
Phase III

Study Objectives:
1. Primary Objective
To confirm the superiority of MR13A9 0.5 μg/kg administered for 4 weeks in improving itching in previously treated hemodialysis patients with pruritus versus placebo in a double-blind design.
2. Secondary Objectives
1) To determine the efficacy of MR13A9 0.5 μg/kg in improving the following in previously treated hemodialysis patients with pruritus:
- Degree of itching
- Itching-related QOL

2) To determine the safety of MR13A9 0.5 μg/kg in previously treated hemodialysis patients with pruritus.

Endpoints:
1. Efficacy endpoints
1) Primary endpoint
Itch NRS score (The primary variable is change from baseline in the mean NRS score at Week 4 of the double-blind 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
- 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

Study Population:
Double-blind period
The double-blind period of 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) Patients providing written informed consent for study participation in person
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 (including the date of informed consent) who can continue hemodialysis without changing its frequency or method (any temporary change in dialysis frequency or method associated with travel or admission to other hospitals with no changes in treatment strategies is acceptable) from the date of informed consent until the end of the follow-up period
4) Patients whose pruritus treatment within 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 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)
- Drugs to treat itching (prescription/nonprescription)
- Moisturizing drugs (prescription/nonprescription)
- Products formulated with any of the above

6) Patients whose NRS score (Appendix 1) in the 7 days prior to the start of the double-blind period (7 days including the

score recorded on the start day of treatment) meets both of the below:
- NRS scores have been recorded for ≥ 5 days.
- The mean value of the recorded scores exceeds 4.0 (not including 4.0).

7) Patients whose itch score based on the Shiratori's severity criteria (Appendix 2) in the 7 days prior to the start of the double-blind period (7 days including the score recorded on the start day of treatment) 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.
8) 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 used nalfurafine hydrochloride within 2 weeks prior to the start of the screening period
4) Patients who received phototherapy to treat itching within 4 weeks prior to the start of the screening period
5) Patients who previously received any study drug (including placebo) in a clinical study of MR13A9
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 with congestive heart failure (NYHA functional class IV) (Appendix 3)
10) Patients with concurrent malignancy or a history of malignancy within 5 years prior to the informed consent procedure
11) Patients with concurrent or previous drug abuse (defined as illicit drug use)
12) Patients with concurrent or previous alcoholism
13) Patients with a history of severe drug hypersensitivity (anaphylactic shock, etc.)
14) Patients with concurrent depression, schizophrenia, or dementia
15) Patients with a concurrent mental disorder 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 studyl device in a clinical study (including clinical studies of medical devices or cellular and tissue-based products) 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 (over at least 1 night) to receive any medical intervention between the informed consent procedure and the end of the follow-up period
20) Patients withdrawn from the study during the screening period because they are found not meeting either of inclusion criteria 6) or 7) after participation in the study
21) Patients withdrawn from the study during the screening period after re-registration
22) Other patients ineligible for study participation in the opinion of the principal investigator or subinvestigator

<u>Extension period</u>

Subjects meeting all of the following criteria for entrance at the Week 6 visit during the double-blind period will enter into the extension period. Subjects not meeting the criteria for entrance will be withdrawn from the study and undergo the assessments at discontinuation promptly.

1) Subjects not withdrawn during the double-blind period
2) Subjects receiving at least 14 doses of the study drug during the double-blind period
3) Subjects completing at least 70% of the symptom diary during the double-blind period
4) Subjects who are not inappropriate to enter into the extension period for safety or other reasons in the opinion of the principal investigator or subinvestigator

Study Design:

- Double-blind period
  A placebo-controlled, multicenter, randomized, double-blind, parallel-group study
- Extension period
  A multicenter, open-label study

Study Drugs:

1. Test drug

- MR13A9 17.5 μg: Pre-filled syringe containing 17.5 μg of MR13A9 per syringe
- MR13A9 25.0 μg: Pre-filled syringe containing 25.0 μg of MR13A9 per syringe
- MR13A9 35.0 μg: Pre-filled syringe containing 35.0 μg of MR13A9 per syringe
- MR13A9 42.5 μg: Pre-filled syringe containing 42.5 μg of MR13A9 per syringe

2. Comparator
- MR13A9 placebo: Pre-filled syringe not containing MR13A9

The MR13A9 placebo is indistinguishable from MR13A9 17.5, 25.0, 35.0, or 42.5 µg.

Dosage and Administration:

1. Screening period

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

2. Double-blind period

In addition to the use of conditionally permitted 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 6 weeks (3 times weekly, 18 times in total). The dose of the study drug will be determined according to Table 1 based on the subject's dry weight before dialysis on the start day of the screening period.

If any dialysis circuit trouble precludes injection through the dialysis circuit, the study drug will be administered directly intravenously. If an extra fourth dialysis session 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	
		0.5 µg/kg group	Placebo group
< 45.0 kg	0.35 mL	17.5 µg	0 µg
≥ 45.0 kg, < 65.0 kg	0.35 mL	25.0 µg	0 µg
≥ 65.0 kg, < 85.0 kg	0.35 mL	35.0 µg	0 µg
≥ 85.0 kg	0.35 mL	42.5 µg	0 µg

3. Extension period

In addition to the use of conditionally permitted 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 52 weeks (3 times weekly, 156 times in total). Study treatment in the extension period will be started at Week 6. The dose of the study drug will be determined according to Table 1, and the dose of the study drug from Week 6 to immediately before Week 34 will be determined based on the subject's dry weight before dialysis at Week 6. The dose of the study drug after Week 34 will be determined based on the subject's dry weight before dialysis at Week 34. The study drug will not be administered at Week 58.

If any dialysis circuit trouble precludes injection through the dialysis circuit, the study drug will be administered directly intravenously. If an extra fourth dialysis session is 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.

4. Follow-up period

A 1-week period after the assessments at discontinuation or a 1-week period after the end of the extension period is defined as the follow-up period, during which subjects will receive no study drug.

Concomitant Treatments:

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. I he dosage and administration of any concomitant medication may be changed for safety reasons including adverse events. Any centrally acting concomitant drug should be used with attention to possible central adverse events.

1. 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, etc.
2) Opioid antagonists	Naloxone hydrochloride, eptazocine hydrobromide, naldemedine tosylate, etc.
3) Investigational products other than MR13A9	Various kinds

2. Conditionally permitted concomitant medications

Between the start of the screening period and the end of the double-blind period (or the time of withdrawal during the double-blind period), subjects may use the drugs listed below that have been used since before the screening period without changing their dosage and administration. In addition, the drugs listed below should not be newly used. The dosage and administration at the start of the screening period should not be changed or newly used.

Between the start of the extension period and the end of the follow-up period, the dosage administration should not be changed or newly used whenever possible.

1) Drugs indicated for the treatment of itching (prescription/nonprescription)
2) Drugs to treat itching (prescription/nonprescription)
3) Moisturizing drugs (prescription/nonprescription)
4) Steroids (excluding inhalants, nasal drops, ear drops, eye drops, and eye ointments)

5) Capsaicin (topical)
6) In-hospital drugs formulated with any of the drugs listed 1) to 5) above
7) Pregabalin, gabapentin
8) Antidepressants, anxiolytics

Among the drugs listed in 1) to 6) above, however, topical use of any prescription/nonprescription drug used to treat itching caused by chronic renal failure or any complication of chronic renal failure will not be restricted (concomitant medications for local itching caused by insect stings, chilblains, contact dermatitis, etc. 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 therapies

Between the start of the screening period and the end of the follow-up period, 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 frequency of dialysis per week and the hemodialysis method (HD, off-line HDF, on-line HDF, or I-HDF) may not be changed. Any temporary change in dialysis frequency or hemodialysis method associated with travel or admission to other hospitals with no changes in treatment strategies is acceptable. The hemodialysis conditions (duration of dialysis and dialyzer) should not be changed whenever possible.

Investigations, Observations, Tests, and Evaluations and their Schedules:

See the study schedule.

Sample Size:

- Double-blind period: The study will enroll 86 subjects each MR13A9 0.5 μg/kg group and the placebo group (172 in total).
- Extension period: The study will enroll 100 subjects who complete 58-week treatment.

Study Schedule

		Screening period			Double-blind period				Extension period									Follow-up period
Visit (weeks after initial dose)		**Week−2**	**Week−1**	**Initial dose**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 7**	**Week8**	**Week 10**	**Week 12**	**Week 18**	**Week 26**	**Week 34**	**Week 46**	**Week 58**	**Week 59**
Acceptable time window [a]		—	—	—	—	—	—	—	—	—	—	—	Week 17–19	Week 25–27	Week 33–35	Week 45–47	Week 57–59	—
Visit		1	—	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Day of the week [a]		Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue	Mon/Tue
Informed consent	●																	
Eligibility assessment	●	●		●				●										
Subject demographics	●	●		●														
Subject registration	Primary	Secondary		Tertiary				Entering into the extension period										
Study treatment [b]				→	→	→	→	→	→	→	→	→	→	→	→	→		
Confirmation of DW/dose		●						●							●			
NRS [c] Shiratori's severity criteria [c]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Skindex-16 5-D itch scale				●			●				●		●	●	●	●	●	
PGIC							●				●		●	●	●	●	●	
Vital signs [d] Laboratory tests [d]		●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Postdialysis BUN Postdialysis weight		●																
Serum pregnancy test [e]		●															●	
Body weight [d] 12-lead ECG [d]		●		●				●				●			●		●	
Dependency assessment													●[d]		●[d]		●[d]	●
Adverse events Concomitant medications/therapies		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Specific signs/symptoms			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Prohibited concomitant medications Prohibited concomitant therapies Hemodialysis method		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Conditionally permitted concomitant medications		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

a) Assessments and tests will be performed on the day of first dialysis of each week (Monday or Tuesday).
b) The study drug will not be administered in Week 58.
c) Subjects will record these data in the symptom diary once daily from the next day of the start date of the screening period until the end of the follow-up period.
d) To be performed before dialysis.
e) To be performed only in women of childbearing potential (within 1 year of their last menstrual period and who have not undergone hysterectomy or bilateral total ovariectomy).

Study Schedule (at the time of discontinuation)

	Double-blind period or extension period	Follow-up period [f]
Visit (weeks after initial dose)	At discontinuation	Week 1 after discontinuation
Visit	—	—
Day of the week	— [e]	— [g]
Informed consent		
Eligibility assessment		
Subject demographics		
Subject registration [a]	●	
Study treatment		
Confirmation of DW/dose		
NRS [b] Shiratori's severity criteria [b]	→	→
Skindex-16 5-D itch scale	●	
PGIC	●	
Vital signs [c] Laboratory tests [c]	●	
Postdialysis BUN Postdialysis weight		
Serum pregnancy test [d]	●	
Body weight [c] 12-lead ECG [c]	●	
Dependency assessment	● [c]	●
Adverse events Concomitant medications/therapies	→	→
Specific signs/symptoms	→	→
Prohibited concomitant medications Prohibited concomitant therapies Hemodialysis method	→	→
Conditionally permitted concomitant medications	→	→

a) To be performed only in subjects withdrawing from the study during the double-blind period.
b) Subjects will record these data in the symptom diary once daily until the end of the follow-up period.
c) To be performed before dialysis.
d) To be performed only in women of childbearing potential (within 1 year of their last menstrual period and who have not undergone hysterectomy or bilateral total ovariectomy).
e) Assessments and tests will be performed on the next dialysis day after discontinuation has been decided.
f) Excluding those withdrawing from the study during the screening period.
g) To be performed on the same day of the week as the day of the assessments at discontinuation.

Table of Contents

List of Abbreviations and Terms

Abbreviation/Term	Definition
AUC_{0-x}	Area under the plasma concentration-time curve from time zero to x hours
C_{max}	Maximum plasma concentration
CYP	Cytochrome P450
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
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. Subsequently, a phase II clinical study in hemodialysis patients was conducted to investigate the dose-response relationship for the efficacy and safety of MR13A9. There was a dose-response relationship showing a constant effect of MR13A9 at doses of 0.5 μg/kg and higher, indicating that the recommended clinical dose was 0.5 μg/kg. Based on these results, this phase III clinical study has been planned to confirm the superiority of MR13A9 0.5 μg/kg to placebo as well as to confirm its long-term safety.

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.

In a 26-week repeated subcutaneous dose carcinogenicity study of MR13A9 in mice and a 2-year repeated subcutaneous dose carcinogenicity study in rats, MR13A9 was not carcinogenic in mice or rats.

1.3.2 Clinical study results

1.3.2.1 Clinical pharmacology studies

In a Japanese clinical pharmacology study in 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. The $t_{1/2}$ of MR13A9 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 Japanese clinical pharmacology study in healthy 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 an overseas clinical pharmacology study in 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.

In an overseas QT/QTc evaluation study (CR845-100201), 58 healthy adults (26 males and 32 females) received a single dose of MR13A9 0.5 or 3.0 μg/kg, placebo, or moxifloxacin 400 mg. The upper limit of the 90% confidence interval of ΔΔQTcF in the MR13A9 0.5 and 3.0 μg/kg groups was below 10 msec at all time points. No clinically significant QTc interval prolongation was observed at any dose.

In an overseas mass balance study (CR845-100302), a single dose of [^{14}C]-MR13A9 was administered to 6 healthy adults (males) and 6 hemodialysis patients (males). In the healthy adults, [^{14}C]-MR13A9 was excreted mainly in urine, and 80.5% and 11.3% of radioactivity were recovered in urine and feces, respectively. In the hemodialysis patients, [^{14}C]-MR13A9 was excreted mainly in feces, and 11.2%, 58.8%, and 19.5% of radioactivity were recovered in urine, feces, and dialysate, respectively. In the healthy adults and hemodialysis patients, over 99% of MR13A9 was present as unchanged drug in their plasma. In addition, no metabolites detected in urine or feces accounted for more than 10% of the administered dose in any subject group.

1.3.2.2 Efficacy and safety

In a Japanese phase II clinical study (MR13A9-3), 105 previously treated hemodialysis patients with pruritus received MR13A9 0.25, 0.5, 1.0, or 1.5 μg/kg, or placebo injected into the venous line of the dialysis circuit at the end of each dialysis session 3 times weekly for 2 weeks. 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) suggested a dose-dependent improvement by treatment with MR13A9 at doses ≥ 0.5 μg/kg. Common 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. 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 Japanese phase II clinical study (MR13A9-4), 247 previously treated hemodialysis patients with pruritus received MR13A9 0.25, 0.5, or 1.0 μg/kg, or placebo injected into the venous line of the dialysis circuit at the end of each dialysis session 3 times weekly for 8 weeks. The primary variable of change from baseline in the mean NRS score at Week 8 of the treatment period (adjusted mean ± standard error) was −2.97 ± 0.29 in the MR13A9 0.25 μg/kg group, −3.65 ± 0.30 in the 0.5 μg/kg group, and −3.64 ± 0.30 in the 1.0 μg/kg group, compared with −2.86 ± 0.29 in the placebo group. These results showed significant

improvement in the MR13A9 0.5 and 1.0 μg/kg groups compared with the placebo group, indicating a dose-response relationship showing a constant effect at doses of ≥ 0.5 μg/kg. Adverse drug reactions reported in ≥ 3% of subjects in any group during the treatment period included somnolence, dizziness, palpitations, vomiting, nausea, and blood thyroid stimulating hormone decreased. Study treatment was discontinued or interrupted due to 5 events in 4 of 61 subjects in the MR13A9 0.5 μg/kg group and 6 events in 5 of 62 subjects in the 1.0 μg/kg group. Dependency was assessed as being absent in all evaluable subjects.

In an overseas phase II clinical study (CR845-CLIN2101), 174 hemodialysis patients with moderate to severe pruritus received MR13A9 0.5, 1.0, or 1.5 μg/kg, or placebo injected into the venous line of the dialysis circuit at the end of each dialysis session 3 times weekly for 8 weeks. The primary endpoint of change from baseline in the weekly mean 24-hour Worst Itching Intensity NRS score at the final week of the treatment period (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 in the placebo group. 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.

In the verification part of an overseas phase III clinical study (CR845-CLIN3102), 377 hemodialysis patients with moderate to severe pruritus received MR13A9 0.5 μg/kg or placebo injected into the venous line of the dialysis circuit at the end of each dialysis session 3 times weekly for 12 weeks. The primary endpoint of proportion of subjects with a ≥ 3 points improvement in NRS score (Week 12) was 51.0% in the MR13A9 0.5 μg/kg group and 27.6% in the placebo group. MR13A9 0.5 μg/kg group showed significant improvement compared with the placebo group. The incidence of adverse drug reactions was 5.3% (10/188 subjects) in the placebo group and 6.9% (13/188 subjects) in the 0.5 μg/kg group. Common adverse drug reactions (reported in ≥ 1% of the subjects in the MR13A9 group) included dizziness, somnolence, constipation, headache, hypoaesthesia, paraesthesia, and confusional state.

1.4 Summary of Expected Adverse Drug Reactions and Benefits

1.4.1 Expected adverse drug reactions

In the Japanese phase II clinical study (MR13A9-3), 84 patients received MR13A9 0.25, 0.5, 1.0, or 1.5 μg/kg injected into the venous line of the dialysis circuit at the end of each dialysis session 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.

In the Japanese phase II clinical study (MR13A9-4), 184 patients received MR13A9 0.25, 0.5, or 1.0 μg/kg injected into the venous line of the dialysis circuit at the end of each dialysis session 3 times weekly for 8 weeks. Adverse drug reactions reported in ≥ 3% of subjects in any of the MR13A9 groups included somnolence, dizziness, palpitations, vomiting, nausea, and blood thyroid stimulating hormone decreased.

In the overseas phase II clinical study (CR845-CLIN2101), 129 patients received MR13A9 0.5, 1.0, or 1.5 μg/kg injected into the venous line of the dialysis circuit at the end of each dialysis session 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 the overseas phase III clinical study (verification part of CR845-CLIN3102), 188 patients received MR13A9 0.5 μg/kg injected into the venous line of the dialysis circuit at the end of each dialysis session 3 times weekly for 12 weeks. Adverse drug reactions reported in ≥ 1% of subjects in the MR13A9 group included dizziness, somnolence, constipation, headache, hypoaesthesia, paraesthesia, and confusional state.

In overseas 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 the Japanese phase I clinical study in healthy 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 overseas 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 III clinical study of MR13A9 in previously treated hemodialysis patients with pruritus

2.2 Development Phase

Phase III

3. Study Objectives

3.1 Primary Objective

To confirm the superiority of MR13A9 0.5 μg/kg administered for 4 weeks in improving itching in previously treated hemodialysis patients with pruritus versus placebo in a double-blind design.

3.2 Secondary Objectives

1) To determine the efficacy of MR13A9 0.5 μg/kg in improving the following in previously treated hemodialysis patients with pruritus:
   - Degree of itching
   - Itching-related QOL
2) To determine the safety of MR13A9 0.5 μg/kg in previously treated hemodialysis patients with pruritus.

4. Endpoints

4.1 Endpoints for Efficacy

4.1.1 Efficacy endpoints

4.1.1.1 Primary endpoint

Itch NRS score (The primary variable is change from baseline in the mean NRS score at Week 4 of the double-blind period.)*

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

4.1.1.2 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)

4.1.2 Rationale for the efficacy endpoints

4.1.2.1 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.

4.1.2.2 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.

4.2 Endpoints for Safety

4.2.1 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 ECG
- Dependency assessment

4.2.2 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.

5. Study Population

5.1 Double-blind period

The double-blind period of this study will enroll previously treated hemodialysis patients with pruritus who meet all of the inclusion criteria and none of the exclusion criteria below.

5.1.1 Inclusion criteria

1) Patients aged 20 years or older (at the time of signing informed consent)
2) Patients providing written informed consent for study participation in person

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 (including the date of informed consent) who can continue hemodialysis without changing its frequency or method (any temporary change in dialysis frequency or method associated with travel or admission to other hospitals with no changes in treatment strategies is acceptable) from the date of informed consent until the end of the follow-up period

4) Patients whose pruritus treatment within 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 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)
   - Drugs to treat itching (prescription/nonprescription)
   - Moisturizing drugs (prescription/nonprescription)
   - Products formulated with any of the above

6) Patients whose NRS score in the 7 days prior to the start of the double-blind period (7 days including the score recorded on the start day of treatment) (Appendix 1) meets both of the below:

   - NRS scores have been recorded for ≥ 5 days.
   - The mean value of the recorded scores exceeds 4.0 (not including 4.0).

7) Patients whose itch score based on the Shiratori's severity criteria (Appendix 2) in the 7 days prior to the start of the double-blind period (7 days including the score recorded on the start day of treatment) 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.

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

5.1.2 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)-7) To include patients who have a certain degree of itching continuously.

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

5.1.3 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 used nalfurafine hydrochloride within 2 weeks prior to the start of the screening period

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

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

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 with congestive heart failure (NYHA functional class IV) (Appendix 3)

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

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

12) Patients with concurrent or previous alcoholism

13) Patients with a history of severe drug hypersensitivity (anaphylactic shock, etc.)

14) Patients with concurrent depression, schizophrenia, or dementia

15) Patients with a concurrent mental disorder 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 study device in a clinical study (including clinical studies of medical devices or cellular and tissue-based products) 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 (over at least 1 night) to receive any medical intervention between the informed consent procedure and the end of the follow-up period

20) Patients withdrawn from the study during the screening period because they are found not meeting either of inclusion criteria 6) or 7) after participation in the study

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

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

5.1.4 Rationale for the exclusion criteria

1)-5)	To perform the efficacy evaluation of MR13A9 appropriately.
6)-13), 19), 21), 22)	To ensure the safety of subjects.
14), 15)	To exclude the effect of this condition on protocol adherence.
16)	To ensure the safety of pregnant women, fetuses, and infants because the safety of MR13A9 in them has not been established.
17)	To ensure the safety of female partners of childbearing potential and female partners who are pregnant 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 an ethical aspect.
20)	Re-registration will not be permitted because it could affect the efficacy evaluation.

5.2 Extension Period

Subjects meeting all of the following criteria for entrance at the Week 6 visit during the double-blind period will enter into the extension period. Subjects not meeting the criteria for entrance will be withdrawn from the study and undergo the assessments at discontinuation promptly.

5.2.1 Criteria for entrance

1) Subjects not withdrawn during the double-blind period

2) Subjects receiving at least 14 doses of the study drug during the double-blind period

3) Subjects completing at least 70% of the symptom diary during the double-blind period

4) Subjects who are not inappropriate to enter into the extension period for safety or other reasons in the opinion of the principal investigator or subinvestigator

5.2.2 Rationale for the criteria for entrance

1), 2) To perform the efficacy evaluation of MR13A9 appropriately.

3) To include subjects who can perform appropriate assessment using a symptom diary.

4) To ensure the safety of subjects.

5.3 Discontinuation of Individual Subjects

5.3.1 Discontinuation criteria (discontinuation of individual subjects)

1) Adverse events

- 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 (between the date of informed consent and the end of the follow-up period)

- Any GCP violation is found
- After the initial study treatment, the subject is found not meeting any of the inclusion criteria or meeting any of the exclusion criteria stipulated in the protocol
- A subject has received the study drug with drug number other than specified

5) Four consecutive missed doses of the study drug during the double-blind period

6) Seven consecutive missed doses of the study drug during the extension period

7) Not meeting the criteria for entrance at the Week 6 visit of the double-blind period

8) Pregnancy

9) Discontinuation of the entire study

10) Discontinuation of the study at the study site

11) Lost to observation or follow-up

- Study continuation becomes impossible because of failure to contact the subject.

12) 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)

5.3.2 Responses to the discontinuation of any individual subject

- If a subject meets any of the criteria described in "5.3.1 Discontinuation criteria (discontinuation of individual subjects)" during the study, the principal investigator or subinvestigator will immediately decide to discontinue the study. On the next dialysis day 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 during the double-blind period or the extension period, the next day of the assessments at discontinuation will be regarded as the start date of the follow-up period.
- 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 "10.13.9 Follow-up investigation."
- If a subject does not return to the study site, the principal investigator, subinvestigator, or clinical research coordinator will immediately investigate the reason for missed visits and the subsequent course.

6. Subject Consent

6.1 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).

6.2 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) in advance.

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.

7. Study Drugs

7.1 Test Drug and Comparator

7.1.1 Test drug

1) Code name: MR13A9
2) Nonproprietary name: Difelikefalin acetate (JAN)
3) Strength and dosage form:
   - MR13A9 17.5 μg: Pre-filled syringe containing 17.5 μg of MR13A9 per syringe
   - MR13A9 25.0 μg: Pre-filled syringe containing 25.0 μg of MR13A9 per syringe
   - MR13A9 35.0 μg: Pre-filled syringe containing 35.0 μg of MR13A9 per syringe
   - MR13A9 42.5 μg: Pre-filled syringe containing 42.5 μg of MR13A9 per syringe
4) Storage conditions: Store at room temperature (1°C to 30°C)

7.1.2 Comparator

1) Strength and dosage form:

MR13A9 placebo: Pre-filled syringe not containing MR13A9

The MR13A9 placebo is indistinguishable from MR13A9 17.5, 25.0, 35.0, or 42.5 μg.

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

7.1.3 Rationale for the comparator

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 comparator 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).

7.2 Packaging of the Study Drugs

- Double-blind period

A total of 21 prefilled syringes containing MR13A9 0.5 μg/kg or placebo packaged in blister packs (18 syringes for 6-week treatment + 3 spare syringes) will be packed in 1 carton.

- Extension period

A total of 10 prefilled syringes containing MR13A9 0.5 μg/kg packaged in blister packs (9 syringes for 3-week treatment + 1 spare syringe) will be packed in 1 carton.

7.3 Labeling

Details of labeling will be provided in a separate written procedure.

7.4 Management of the Study Drugs

The study drug manager will manage and store the study drugs appropriately, as stipulated separately in the written procedure.

8. Study Methods

8.1 Study Design

- Double-blind period

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

- Extension period

A multicenter, open-label study

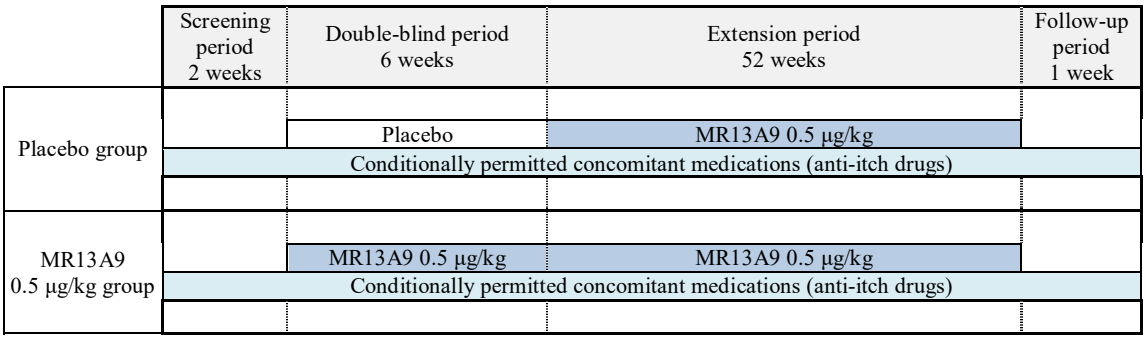

Figure 8.1-1 Study Design

8.2 Dosage and Administration

8.2.1 Screening period

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

8.2.2 Double-blind period

In addition to the use of conditionally permitted 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 6 weeks (3 times weekly, 18 times in total). The dose of the study drug will be determined based on the subject's dry weight before dialysis on the start day of the screening period according to Table 8.2.2-1.

If any dialysis circuit trouble precludes injection through the dialysis circuit, the study drug will be administered directly intravenously. If an extra fourth dialysis session is 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 8.2.2-1 Doses

Dry weight	Injected volume	MR13A9 dose	
		0.5 μg/kg group	Placebo group
< 45.0 kg	0.35 mL	17.5 μg	0 μg
≥ 45.0 kg, < 65.0 kg	0.35 mL	25.0 μg	0 μg
≥ 65.0 kg, < 85.0 kg	0.35 mL	35.0 μg	0 μg
≥ 85.0 kg	0.35 mL	42.5 μg	0 μg

8.2.3 Extension period

In addition to the use of conditionally permitted 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 52 weeks (3 times weekly, 156 times in total). Study treatment in the extension period will be started at Week 6. The dose of the study drug will be determined according to Table 8.2.2-1, and the dose of the study drug from Week 6 to immediately before Week 34 will be determined based on the subject's dry weight before dialysis at Week 6. The dose of the study drug after Week 34 will be determined based on the subject's dry weight before dialysis at Week 34. The study drug will not be administered at Week 58.

If any dialysis circuit trouble precludes injection through the dialysis circuit, the study drug will be administered directly intravenously. If an extra fourth dialysis session is 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.

8.2.4 Follow-up period

A 1-week period after the assessments at discontinuation or a 1-week period after the end of the extension period is defined as the follow-up period, during which subjects will receive no study drug.

8.2.5 Rationale for the doses and the duration of treatment

In a Japanese phase II clinical study (Study MR13A9-4), intravenous administration of MR13A9 0.25, 0.5, and 1.0 μg/kg or placebo 3 times weekly for 8 weeks resulted in significant improvement of pruritus in 0.5 and 1.0 μg/kg groups compared with the placebo group. In addition, there was a dose-response relationship showing a constant effect of MR13A9 at doses of 0.5 μg/kg and higher. As for safety, MR13A9 at up to 1.0 μg/kg was tolerated, but adverse events occurred frequently in the 1.0 μg/kg group. The phase II study in the United State (Study CLIN2101) and phase III study (Study CLIN3102) also confirmed the superiority of the MR13A9 0.5 μg/kg group to the placebo group. Based on the above, it was considered appropriate to select 0.5 μg/kg of MR13A9 as the recommended clinical dose.

In Study MR13A9-4, the effect of MR13A9 to improve itching was constant after Week 4, and all adverse drug reactions occurred before Week 6. Accordingly, 4-week and 6-week periods in the double-blind period were established to allow the efficacy and safety evaluations of MR13A9, respectively. In addition, a 52-week extension period was established to assess the safety of long-term treatment with MR13A9 with reference to the "Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" (ELD Notification No. 592 dated May 24, 1995).

8.3 Concomitant Treatments

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. The dosage and administration of any concomitant medication may be changed for safety reasons including adverse events. Any centrally acting concomitant drug should be used with attention to possible central adverse events.
A summary of concomitant treatments is shown in Table 8.3-1.

Table 8.3-1 Concomitant Treatments

	Screening period	Double-blind period	Extension period	Follow-up period
Concomitant medications	Permitted (The dosage and administration should not be changed whenever possible.)			
Prohibited concomitant medications	Not permitted			
Conditionally permitted concomitant medications	Permitted (The dosage and administration should not be changed or newly used.)		Permitted (The dosage and administration should not be changed or newly used whenever possible.)	
Prohibited concomitant therapies	Not permitted			

8.3.1 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 8.3.1-1 will be prohibited.

Table 8.3.1-1 Prohibited concomitant medications

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

8.3.2 Conditionally permitted concomitant medications

Between the start of the screening period and the end of the double-blind period (or the time of withdrawal during the double-blind period), subjects may use the drugs listed below that have been used since before the screening period without changing their dosage and administration. In addition, the drugs listed below should not be newly used. The dosage and administration at the start of the screening period should not be changed or newly used.

Between the start of the extension period and the end of the follow-up period, the dosage administration should not be changed or newly used whenever possible.

1) Drugs indicated for the treatment of itching (prescription/nonprescription)
2) Drugs to treat itching (prescription/nonprescription)
3) Moisturizing drugs (prescription/nonprescription)
4) Steroids (excluding inhalants, nasal drops, ear drops, eye drops, and eye ointments)

5) Capsaicin (topical)

6) In-hospital drugs formulated with any of the drugs listed 1) to 5) above

7) Pregabalin, gabapentin

8) Antidepressants, anxiolytics

Among the drugs listed in 1) to 6) above, however, topical use of any prescription/nonprescription drug used to treat itching caused by chronic renal failure or any complication of chronic renal failure will not be restricted (concomitant medications for local itching caused by insect stings, chilblains, contact dermatitis, etc. 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.

8.3.3 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.

8.3.4 Rationale for the prohibited concomitant medications, conditionally permitted concomitant medications, and prohibited concomitant therapies

To exclude their effects on the efficacy evaluation of MR13A9.

8.4 Hemodialysis Conditions

Between the start of the screening period and the end of the follow-up period, the frequency of dialysis per week and the hemodialysis method (HD, off-line HDF, on-line HDF, or I-HDF) may not be changed. Any temporary change in dialysis frequency or hemodialysis method associated with travel or admission to other hospitals with no changes in treatment strategies is acceptable. The hemodialysis conditions (duration of dialysis and dialyzer) should not be changed whenever possible.

8.5 Randomization and Blinding

8.5.1 Preparation and retention of a treatment assignment table

The person responsible for treatment assignment will prepare a treatment assignment table and retain it until unblinding, as stipulated separately in the written procedure.

8.5.2 Preparation and retention 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 and retain them until unblinding, as stipulated separately in the written procedure.

8.5.3 Subject registration

8.5.3.1 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 "5. 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.

8.5.3.2 Secondary subject registration

The principal investigator or subinvestigator will assess the eligibility of each subject at the start of the screening period (see "5. 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.

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.

8.5.3.3 Tertiary subject registration

The principal investigator or subinvestigator will assess the eligibility of each subject at the start of the double-blind period (see "5. Study Population"), enter necessary information in a tertiary subject registration form, and register the 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.

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.

8.5.3.4 Registration for the extension period

The principal investigator or subinvestigator will assess the eligibility of each subject at the start of the extension period (see "5. Study Population"), enter necessary information in a registration form for the extension period, 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 registration for the extension period of each subject.

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

8.5.3.5 Randomization of subjects

Based on the treatment assignment table prepared by the person responsible for treatment assignment, the subject registration center will randomly assign subjects eligible for tertiary registration to either the MR13A9 0.5 μg/kg or placebo group at a ratio of 1:1 by a dynamic allocation method using two stratification factors: Prior treatment with nalfurafine hydrochloride notified by the medical institution (for ≥ 2 consecutive weeks in the year prior

to the informed consent procedure) and specific signs or symptoms occurring during the screening period (Appendix 4) confirmed before dialysis on the start day of treatment.

8.5.4 Unblinding

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

8.6 Sample size

8.6.1 Sample size

- Double-blind period

The study will enroll 86 subjects each MR13A9 0.5 μg/kg group and the placebo group (172 in total).

- Extension period

The study will enroll 100 subjects who complete 58-week treatment.

8.6.2 Rationale for the sample size

8.6.2.1 Double-blind period

In a Japanese phase II clinical study (MR13A9-4), the change from baseline in the mean NRS score at Week 4 of the treatment period (mean ± standard deviation) was −2.15 ± 1.98 in the placebo group and −3.22 ± 2.09 in the MR13A9 0.5 μg/kg group. The difference for the MR13A9 0.5 μg/kg group versus the placebo group at Week 4 of the treatment period was −1.04 ± 0.35 (adjusted mean ± standard error).

For the primary variable of change from baseline in the mean NRS score at Week 4 of the double-blind period, its mean difference for the MR13A9 0.5 μg/kg group versus the placebo group was assumed to be −1.0, with a common standard deviation of 2.0. Assuming a two-sided significance level of 5% and a statistical power of 90%, the sample size required to confirm the superiority of the MR13A9 0.5 μg/kg group to the placebo group using a two-sample t-test was calculated to be 86 subjects per group.

8.6.2.2 Extension period

With reference to the “The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions” (ELD Notification No. 592 dated May 24, 1995), 100 subjects were assumed to complete 58-week treatment.

9. 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.

2) Pay attention during hazardous machine operation and automobile driving during the treatment period.

3) Maintain the symptom diary in subject every day. Report any device deficiencies to the principal investigator or subinvestigator.

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

5) 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.

6) Visit the study site at the same time at every visit whenever possible during the study period.

7) Report the drug(s) used currently to the principal investigator or subinvestigator before participation in the study. Consult the principal investigator or subinvestigator about any new drug prescribed at other medical departments or hospitals or any over-the-counter drug before use. Report to the principal investigator or subinvestigator immediately if it was inevitable to use any drug without consultation.

8) 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 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.

9) 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 end of the follow-up investigation.

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

11) Men must avoid intercourse 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.

12) 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).

10. Investigations, Observations, Tests, and Evaluations

The principal investigator, subinvestigator, and clinical research coordinator will perform investigations, observations, tests, and evaluations according to the study schedule and the following procedures.

10.1 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) Frequency of dialysis per week at the start of the screening period, hemodialysis methods (HD, off-line HDF, online HDF, I-HDF), and hemodialysis conditions (duration of dialysis, dialyzer)
7) Medical history (any concurrent disease at the time of signing informed consent); if yes, the name of the disease
8) Time of onset of itching associated with chronic renal failure
9) Prior treatment with nalfurafine hydrochloride between 1 year before the time of signing informed consent and the start of the screening period (Week −2); if yes, the duration of treatment and dose
10) Remaining renal function
11) Need for pregnancy testing
12) Information related to the inclusion/exclusion criteria
13) Specific signs or symptoms occurring during the screening period

10.2 Treatment Compliance

Compliance with study treatment (day of dosing and route of dosing) will be recorded in the case report form. Also, the drug number and the dose of the study drug will be recorded in the case report form during the double-blind period and the extension period, respectively.

10.3 Dry Weight

The dry weight before dialysis at Week −2, Week 6, and Week 34 will be recorded in the case report form.

10.4 Concomitant Medications and Concomitant Therapies

10.4.1 Concomitant medications

For all drugs (including over-the-counter drugs) 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 conditionally permitted 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 used for priming and blood return, 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
- Nalfurafine hydrochloride used between the time of informed consent and the start of the screening period (Week −2)

10.4.2 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.

10.5 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 frequency of dialysis per week or 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)]

10.6 Efficacy Endpoints

10.6.1 Symptom diary (electronic diary)

The principal investigator, subinvestigator, or clinical research coordinator will instruct each subject on 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.

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 1, the most severe itching within the day will be recorded in integers 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 2, the symptoms during the day and the night will be recorded on a scale ranging from 0 to 4, where 0 represents no symptoms and 4 represents severe itching.

10.6.2 Skindex-16

At the first visit (before dosing of the study drug) of each week (Monday or Tuesday), 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 recorded

based on a scale ranging from 0 to 6, where 0 represents never bothered and 6 represents always bothered. The date of recording and the result will be recorded in the case report form.

10.6.3 5-D itch scale

At the first visit (before dosing of the study drug) of each week (Monday or Tuesday), subjects will look back on the condition of itching in the past 2 weeks and record the 5 components of itching (duration, degree, direction, disability, distribution) according to Appendix 6. The date of recording and the result will be recorded in the case report form.

10.6.4 PGIC

At the first visit of each week (Monday or Tuesday), subjects will compare the overall symptom of itching with the symptom in the screening period, and record 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. The date of recording and the result will be recorded in the case report form.

10.7 Laboratory Tests

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

10.7.1 Hematology

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

10.7.2 Blood biochemistry

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

10.7.3 Endocrinology

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

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

Systolic blood pressure, diastolic blood pressure, pulse rate, and body temperature will be measured after a period of rest before the first dialysis each week (Monday or Tuesday). 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.

10.9 Body Weight

Body weight will be measured before the first dialysis of each week (Monday or Tuesday). The date and result of measurement will be recorded in the case report form. At the start of the screening period, body weight will also be measured after dialysis, and the date and result of measurement will be recorded in the case report form.

10.10 12-lead ECG

Before dialysis and blood sampling on the first day of each week (Monday or Tuesday), 12-lead ECGs will be obtained in the supine position after a period of rest, and the date of measurement and the assessment by the doctor 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.

10.11 Dependency Assessment

The investigator or subinvestigator will interview each subject using the questionnaire shown in Appendix 8 and record the result of the interview.[18)] The dependency assessment members will perform dependency assessment based on the questionnaire.
Details are stipulated in a separate procedure.

10.12 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.

10.13 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.

10.13.1 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.

10.13.1.1 Adverse event collection period

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

10.13.1.2 Adverse event interview

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?”

10.13.1.3 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.

10.13.2 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

10.13.3 Severity of adverse events

The severity of adverse events will be categorized into 3 grades according to Table 10.13.3-1. For an adverse event in which the severity changes, the highest severity will be recorded.

Table 10.13.3-1 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, and bathing

10.13.4 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.

10.13.5 Adverse events of special interest

On the first dialysis day of each week (Monday or Tuesday) between Week −1 and the end of the follow-up period, 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 4. Then, the principal investigator or subinvestigator will determine and record the presence or absence of specific signs or symptoms occurring in the past week based on the results of interview and the observation of the subject. If any particular sign or symptom is considered to be present, the principal investigator or subinvestigator will determine and record whether the particular sign or symptom is an adverse event. A adverse event of special interest is defined as a specific sign or symptom that is determined to be an adverse event by the principal investigator or subinvestigator. Details are stipulated in a separate procedure.

10.13.6 Action taken with study treatment

Actions taken with study treatment are defined in Table 10.13.6-1.

Table 10.13.6-1 Action taken with study treatment

Action	Definition
Drug withdrawn	Study treatment is discontinued due to the adverse event, including at the subject's request.
Drug Interrupted	Study treatment is interrupted 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 before the onset of the adverse event.

10.13.7 Outcome of adverse events

The outcome of each adverse event will be assessed according to Table 10.13.7-1.

Table 10.13.7-1 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.
Results in death	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.

10.13.8 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 10.13.8-1. Any adverse event occurring after the start of study treatment of which the 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 10.13.8-1 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 a causal relationship with the study drug, specifically when the event falls into one of the following criteria: • 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.

10.13.9 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 any 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 by the end of the follow-up period. The follow-up investigation will be terminated if either of the following criteria is met as a result of the follow-up investigation:

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

11. 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 "10. Investigations, Observations, Tests, and Evaluations."

11.1 At the Time of Signing Informed Consent

- Confirmation of written informed consent
- Confirmation of subject demographics
- Confirmation of eligibility
- Primary subject registration

11.2 Visit 1 (Week −2, at the Start of the Screening Period)

- 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)
- Instructions for the symptom diary
- Confirmation of the dry weight and the dose
- Confirmation of eligibility
- Secondary subject registration

11.3 Visit 2 (Start Day of Administration, at Start of the Double-blind Period)

- Confirmation of subject demographics
- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- 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
- Tertiary subject registration
- Confirmation of the compliance with study treatment

11.4 Visit 3 (Week 1)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Confirmation of the implementation status of hemodialysis
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment

11.5 Visit 4 (Week 2)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Confirmation of the implementation status of hemodialysis
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment

11.6 Visit 5 (Week 4)

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

- Skindex-16
- 5-D itch scale
- PGIC
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment

11.7 Visit 6 (Week 6, at the Start of the Extension Period)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Confirmation of the implementation status of hemodialysis
- Body weight (before dialysis)
- 12-lead ECG
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of eligibility
- Registration for the extension period
- Confirmation of the dry weight and the dose
- Confirmation of the compliance with study treatment

11.8 Visit 7 (Week 7)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Confirmation of the implementation status of hemodialysis
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment

11.9 Visit 8 (Week 8)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Confirmation of the implementation status of hemodialysis
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment

11.10 Visit 9 (Week 10)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Confirmation of the implementation status of hemodialysis
- Skindex-16
- 5-D itch scale
- PGIC
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment

11.11 Visit 10 (Week 12)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Confirmation of the implementation status of hemodialysis
- Body weight (before dialysis)
- 12-lead ECG
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment

11.12 Visit 11 (Week 18)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Dependency assessment (before dialysis)
- Confirmation of the implementation status of hemodialysis
- Skindex-16
- 5-D itch scale
- PGIC
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment

11.13 Visit 12 (Week 26)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies

- Confirmation of the implementation status of hemodialysis
- Skindex-16
- 5-D itch scale
- PGIC
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment

11.14 Visit 13 (Week 34)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Dependency assessment (before dialysis)
- 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)
- Confirmation of the dry weight and the dose
- Confirmation of the compliance with study treatment

11.15 Visit 14 (Week 46)

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Confirmation of the implementation status of hemodialysis
- Skindex-16
- 5-D itch scale
- PGIC
- Vital signs
- Laboratory tests (hematology, blood biochemistry, endocrinology)
- Confirmation of the compliance with study treatment

11.16 Visit 15 (Week 58, at the Start of the Follow-up Period)

- Review of the symptom diary

- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Dependency assessment (before dialysis)
- 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)
- Confirmation of the compliance with study treatment

11.17 Visit 16 (Week 59 [at the End of the Follow-up Period]) or 1 Week after Discontinuation

- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Dependency assessment
- Confirmation of the implementation status of hemodialysis

11.18 At Discontinuation

- Registration for the extension period (only in subjects withdrawing from the study during the double-blind period)
- Review of the symptom diary
- Confirmation of adverse events, concomitant medications, and concomitant therapies
- Dependency assessment (before dialysis)
- 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)
- Confirmation of the compliance with study treatment

12. Measures to Ensure the Safety of the Clinical Study

12.1 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 "10.13.9 Follow-up investigation" will be followed up, as instructed in the section.

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

12.2.1 Action to be taken for serious adverse events

If any serious adverse event described in "10.13.4 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.

12.2.2 Response to serious adverse events

The principal investigator or subinvestigator will notify the sponsor of a serious adverse event within 24 hours of knowledge of its occurrence. In addition, the principal investigator will submit a prespecified document to the sponsor within 3 days, and promptly report the event to the head of the study site, as instructed by the study site's procedure.

12.3 Response to Serious Adverse Events Caused by Device Deficiencies

A device deficiency refers to a deficiency related to quality, safety, performance, etc. in a broad sense such as breakage, malfunction, etc. occurring at the device part of the study drug.
If any serious adverse event caused by a device deficiency occurs, the principal investigator or subinvestigator will respond to it according to "12.2 Action to be Taken for and Response to Serious Adverse Events." If becoming aware of any deficiency that could cause a serious adverse event, the principal investigator will submit a prespecified document to the sponsor within 1 week, and promptly report the deficiency to the head of the study site, as instructed by the study site's procedure.

12.4 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 and has not entered into the extension period.

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. However, it is unnecessary to follow up the subject if she is found to have been in the placebo group after unblinding and has not entered into the extension period.

12.5 Collection and Provision of Safety Information

12.5.1 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.

12.5.2 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 that could affect the safety of subjects or the conduct of the study. 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.

12.6 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.

2) If requested by the principal investigator or subinvestigator to open the emergency key code or if the sponsor considered it necessary to open the emergency key code, the sponsor will open the emergency key code for the drug number, as stipulated separately in the written 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.

13. Discontinuation/Suspension of the Clinical Study

13.1 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.

13.2 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.

13.3 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.

14. Statistical Analysis

Major analysis methods are described below. Details will be specified in a statistical analysis plan prepared separately before the informed consent procedure of the first subject.

For the double-blind period, data from the start of the screening period to the end of the double-blind period will be analyzed. Over the entire study period, data from the start of the screening period to the end of the follow-up period will be analyzed.

Handling of subjects and data in the double-blind period and over the entire study period will be determined before the respective database lock points in the double-blind period and over the entire study period.

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 demographic imbalance. Summary statistics to be presented include 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. Baseline is defined as the start date of treatment.

14.1 Analysis Sets

Analysis sets are defined as follows: When the full analysis set (FAS) and the per protocol set (PPS) are used as analysis sets, analyses will be performed based on the treatment to which each subject has been assigned. When the safety set (SS) is used as an analysis set, analyses will be performed based on the treatment provided to each subject actually.

1) FAS
   Population of subjects given at least one dose of the study drug, meeting the inclusion criterion related to NRS score, and having a baseline mean NRS score.
2) PPS (only in the double-blind period)
   Population of subjects excluding the following subjects from the FAS:
   - Subjects not meeting the inclusion criteria
   - Subjects meeting any of the exclusion criteria related to efficacy evaluation
   - Subjects withdrawing from the study before Week 4 in the double-blind period
   - Subjects given < 9 or > 15 doses of the study drug before Week 4 in the double-blind period
   - Subjects changing the dosage and administration of a conditionally permitted concomitant medication or newly using a conditionally permitted concomitant medication before Week 4 in the double-blind period
   - Subjects using a prohibited concomitant drug or therapy before Week 4 in the double-blind period
   - Subjects changing the frequency of dialysis per week or the hemodialysis method before Week 4 in the double-blind period

3) SS
Population of subjects given at least one dose of the study drug

14.2 Analysis Groups

14.2.1 Double-blind period

The analysis sets and subjects included in the analysis sets for the analysis groups are shown in Table 14.2.1-1.

Table 14.2.1-1 Analysis sets and subjects included in the analysis sets for the analysis groups

Analysis Groups	Analysis Sets	Subjects included in the analysis set
MR13A9 0.5 μg/kg group	FAS, PPS	Subjects randomized to MR13A9 0.5 μg/kg
	SS	Subjects given MR13A9 0.5 μg/kg
Placebo group	FAS, PPS	Subjects randomized to placebo
	SS	Subjects given placebo

14.2.2 Entire study period

The analysis sets and subjects included in the analysis sets for the analysis groups are shown in Table 14.2.2-1.

Table 14.2.2-1 Analysis sets and subjects included in the analysis sets for the analysis groups

Analysis Groups	Analysis Sets	Subjects included in the analysis set
MR-MR group	FAS	Subjects randomized to MR13A9 0.5 μg/kg in the double-blind period and entering into the extension period
	SS	Subjects given MR13A9 0.5 μg/kg in the double-blind period and entering into the extension period
P-MR group	FAS	Subjects randomized to placebo in the double-blind period and entering into the extension period
	SS	Subjects given placebo in the double-blind period and entering into the extension period

14.3 Disposition of Subjects

For each analysis set and the presence/absence of discontinuation, numbers and percentages of subjects will be presented. For the double-blind period, differences between the groups will be examined.

14.4 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. For the double-blind period, imbalance between the groups will be examined.

14.5 Efficacy

The FAS will be used as the primary analysis set for the double-blind period. 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.

The FAS will be used as the analysis set for the entire study period.

14.5.1 Primary endpoint

The primary endpoint is the NRS score. The assessment time points and their time windows in the screening period, the double-blind period, and the extension period are shown in Table 14.5.1-1. The assessment time point and its time window in the follow-up period are shown in Table 14.5.1-2.

Table 14.5.1-1 Assessment time points and their time windows in the screening period, the double-blind period, and the extension period

Period	Assessment time point	Assessment time window [a)]
Screening period	At Week −1	From Day −13 to Day −7
Double-blind period	At baseline	From Day −6 to Day 1
	At Weeks 1 to 6	From Day 7 × x − 5 to Day 7 × x + 1 [b)]
Extension period	At Weeks 7 to 58	From Day 7 × x − 5 to Day 7 × x + 1 [b)]

a) The start date of the double-blind period will be regarded as Day 1 and the previous day of the start date of the double-blind period will be regarded as Day −1.
b) x: Number of weeks

Table 14.5.1-2 Assessment time point and its time window in the follow-up period

Period	Assessment time point	Assessment time window [a)]
Follow-up period	At Week 1 of the follow-up period	From Day 1 to Day 7

a) The start date of the follow-up period (the completion date of the extension period 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. However, if the number of observation days during the assessment period is less than 4 days at the time of calculation of the score at each time point, the data will be deemed as missing:

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

14.5.2 Primary variable

The primary variable will be the change from baseline in the mean NRS score at Week 4 of the double-blind period.

14.5.3 Analysis of the primary variable

Data obtained up to Week 4 of the double-blind period will be analyzed.

14.5.3.1 Primary analysis

The superiority of the MR13A9 0.5 μg/kg group to the placebo group will be confirmed by performing the analysis 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 the presence or absence of prior treatment with nalfurafine hydrochloride as a dynamic allocation factor as covariates; and subject as a random effect.

The analysis will include all available data obtained at each time point from Week 1 to Week 4 of the double-blind period as objective variables. 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 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.

The adjusted mean change at each time point for each group and its two-sided 95% confidence interval will be presented. The adjusted mean difference in the change at each time point between the placebo group and the MR13A9 0.5 μg/kg group and its two-sided 95% confidence interval as well as the p value will be presented.

14.5.3.2 Sensitivity analysis

Sensitivity analyses 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 analyses, treatment effects will be estimated as in the primary analysis.

1) MI – MMRM

Multiple imputed data will be generated in the 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 the baseline and Week 4 of the double-blind 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 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 the baseline and Week 4 of the double-blind 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.

14.5.3.3 Other assessment variables

1) Change from baseline in the mean NRS score

Summary statistics will be presented. A one-sample t-test will be used for comparisons within each group. For the double-blind period, a two-sample t-test will be used for comparisons between the placebo group and the MR13A9 0.5 μg/kg group.

2) Mean NRS score

Summary statistics will be presented.

3) Percentage of subjects with improvement in the mean NRS score

The number and percentage of subjects with improvement in the mean NRS score will be presented. For the double-blind period, a Fisher's exact test will be used for comparisons between the placebo group and the MR13A9 0.5 μg/kg group. Subjects with improvement are defined as shown below.

- Subjects with 3-point improvement: Change from baseline in the mean NRS score is ≤ -3
- Subjects with 4-point improvement: Change from baseline in the mean NRS score is ≤ -4

14.5.4 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 "14.5.1 Primary endpoint."

For changes from baseline, the same analysis as "14.5.3.1 Primary analysis" will be performed on the data obtained up to Week 4 of the double-blind period. However, the covariate of the model will be the baseline of the data to be analyzed. The same analysis as "14.5.3.3 1) Change from baseline in the mean NRS score" will be performed.

For measurements, the same analysis as "14.5.3.3 2) Mean NRS score" will be performed.

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

For changes from baseline, analysis of covariance with treatment group as a fixed effect and baseline score as a covariate will be performed on the data obtained at the end of the double-blind period. The same analysis as "14.5.3.3 1) Change from baseline in the mean NRS score" will be performed.

For measurements, the same analysis as "14.5.3.3 2) Mean NRS score" will be performed.

3) PGIC(Patient Global Impression of Change)

The number and percentage of subjects with global symptoms will be presented. For the double-blind period, a two-sample Wilcoxon test will be used for comparisons between the placebo group and the MR13A9 0.5 μg/kg group.

14.6 Safety

The SS will be used as the analysis set.

14.6.1 Adverse events and adverse drug reactions

For the double-blind period, analysis will include events occurring between the start of study treatment in the double-blind period and the end of the double-blind period. For the entire study period, analysis will include events occurring between the start of study treatment in the double-blind period and the end of the follow-up period.

Adverse events of special interest will also be summarized in the same manner.

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. For the double-blind period, a Fisher's exact test will be used for comparisons between the placebo group and the MR13A9 0.5 μg/kg group, and the between-group difference in incidence and its 95% confidence interval will be presented.

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

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

5) Occurrence of adverse events and adverse drug reactions (by time of onset)

For the entire study period, the number of subjects experiencing events and the incidence of events for all events and by primary SOC and PT will be presented by time of onset.

14.6.2 Vital signs and body weight

Summary statistics as well as scatter plots before and after treatment will be presented.

14.6.3 Laboratory tests

For quantitative values, summary statistics as well as scatter plots and shift tables before and after treatment will be presented.

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

14.6.4 Dependency assessment

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

14.7 Timing of Analyses

When all data obtained in the double-blind period are locked, an interim analysis of the data in the double-blind period will be performed. When data obtained up to Week 34 of the extension period are locked, interim tabulation of the data up to Week 34 will be performed. When all data obtained in the extension period are locked, the final tabulation of the data over the entire study period will be performed.

15. Compliance with the Protocol, etc.

15.1 Agreement on the Protocol

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

15.2 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.

15.3 Deviation from the Protocol

The principal investigator or subinvestigator will document all deviations 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.

16. Direct Access to Source Documents

16.1 Source Documents and Source Data

"Source documents" refer to information on the course of events in the study as well as 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.

"Source data" refer to all information recorded in the original records on clinical findings, observations, and other activities in a clinical study and their certified copies, which are necessary for the reconstruction and evaluation of the course of events in the clinical study. "Source data" are contained in the source documents (original records or their certified copies).

Source data must be attributable, legible, contemporaneous, original, accurate, and complete, and any changes made to the source data may be traceable and may not obscure the original entry.

16.2 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.

16.3 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.

17. 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.

18. Ethics

18.1 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.

18.2 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.

18.3 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.

19. Data Handling, and Record Keeping

19.1 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 double-blind period, at least the information on the date of written informed consent, sex, year and month of birth, race, adverse events, and discontinuation of the study will be collected and recorded in the case report form. Case report forms will be completed as instructed separately in the written procedure.

19.2 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. The symptom diary will be recorded as instructed separately in the written procedure.

19.3 Submission of 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 submit copies of all ECG charts for the subject obtained during the study to the sponsor.

19.4 External Data

If obtaining any measurements at an external laboratory testing facility as electronic data, the sponsor will obtain such 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.

19.5 Record Keeping

19.5.1 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.

19.5.2 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.

19.5.3 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.

20. 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.

21. 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.

22. Study Administrative Structure

This study will be planned and conducted by the organizations described in the separate volume of the protocol. The separate volume will be revised separately from this protocol.

23. History of Protocol Amendments

Version: 1.0: created on October 28, 2020

24. Literature References

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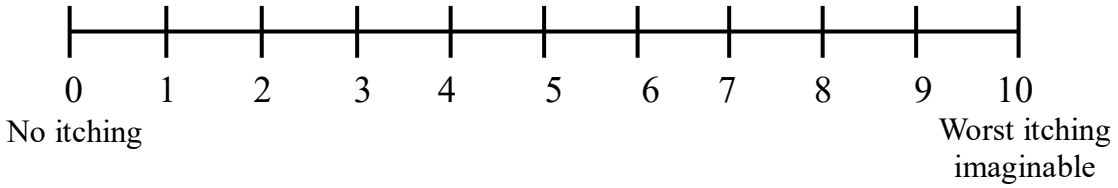
25. Appendices

Appendix 1 NRS (numerical rating scale)



Appendix 2 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 3 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 4 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 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 are categorized into questions concerning symptoms, No. 5 to 11 are categorized into questions concerning emotions, and No. 12 to 16 are categorized into questions concerning functioning. Patients choose one 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?
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 Weeks 18, 34, and 58 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 59 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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