Gabapentin Enacarbil Post-marketing Clinical Study Protocol

- A Randomized, Double-blind, Placebo-controlled, Parallel-group Study in Subjects With Restless Legs Syndrome -

ISN/Protocol 8825-CL-0101

Version 3.0

13 January 2017

(Translation from Japanese)

Sponsor:

Astellas Pharma Inc.(API)

2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo

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I SIGNATURE

AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This clinical study will be conducted in adherence to GCP, GPSP, ICH Guidelines and applicable laws and regulatory requirements, as well as this study protocol. As the evidence of the agreement, the investigator and responsible person of the Sponsor inscribe in the bipartite agreement by signature or "printed name and seal."

II CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

Contact Information for the Sponsor

Corporate Name: Astellas Pharma Inc.

Location: 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo

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Fax: [redacted]

Sponsor's personnel: [redacted], [redacted], [redacted], [redacted], [redacted]

[Contact numbers during non-business hours and for emergency]

Sponsor contact personnel: [redacted]

Contact Information for the Contract Research Organization (CRO)

Corporate name: [redacted]

Location: [redacted]

Phone No.: [redacted]

Fax: [redacted]

CRO's person: [redacted]

[Contact numbers during non-business hours and for emergency]

CRO contact personnel: [redacted]

III LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERM

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
AST	Aspartate Aminotransferase (GOT)
AUCinf	AUC from the time of dosing up to infinity with extrapolation of the terminal phase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C_{max}	Maximum plasma concentration
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA-2K	Ethylenediaminetetraacetic acid dipotassium salt
EQ-5D-5L	EuroQol-5Dimension-5 Level
FAS	Full Analysis Set
Free T_4	Free thyroxine
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GPSP	Good Post-marketing Study Practice
γ-GTP	γ-glutamyltranspeptidase
ICGI	Investigator-rated Clinical Global Impression
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDF	Iyakuhinmei Data File
IRB	Institutional Review Board
IRLS	International Restless Legs Syndrome Rating Scale
IRT	Interactive Response Technology (used for subject registration)
ISN	International Study Number
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities/Japanese version
MITT	Modified Intention-to-Treat
NGSP	National Glycohemoglobin Standardization Program (HbA1c reporting units)
PCGI	Patient-rated Clinical Global Impression: Patient-rated Clinical Global Impression
PPS	Per Protocol Set

Abbreviations	Description of abbreviations
PT	Preferred Term
QOL	Quality Of Life
RBC	Red Blood Cell
RLS	Restless Legs Syndrome
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SDV	Source Document Verification
SMO	Site Management Organization
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total Bilirubin
TSH	Thyroid Stimulating Hormone
WBC	White Blood Cell

Definition of Key Study Terms

Term	Definition of terms
Follow-up period	The period from the start of administration of the study drug for the follow-up period to the final observation
Gabapentin	An antiepileptic drug synthesized in Germany in 1973; the active metabolite of gabapentin enacarbil
Gabapentin enacarbil	The active substance of Regnite Tablets; nonproprietary name of the drug
Registration failure	A subject who provided informed consent but did not fulfill the inclusion/exclusion criteria for formal registration and thus was not randomized or did not receive open-label study drug, or who withdrew consent during the run-in period.
Study period	The period from informed consent of the subject to completion of protocol-specified last evaluation/observation in the subject
Screening	A process of active consideration of potential subjects for enrollment in the study, conducted during the run-in period to determine the eligibility for the study
Enroll	To register or enter a patient into a clinical trial as a subject; NOTE: Once a subject is enrolled into the study, the clinical study protocol applies to the subject.
Subject	Study participant
Subject ID number	A number assigned to a subject who provided consent to participate in the study by signing the consent form
Endpoint	An attribute, phenomenon, or event that varies in quality or quantity and serves as a variable
Baseline	Measurement or finding obtained at a time point judged to be initiation of observation for comparison
Run-in period	The period from the start of administration of the study drug for the run-in period to before the start of administration of the study drug for the treatment period
Randomization	A process of assigning study subjects to treatment or control groups in which an element of chance is used in the determination of assignments to reduce bias
Regnite® Tablets	Alternative name for the study drug gabapentin enacarbil; brand name of the drug product approved for marketing in January 2012
ASP8825	Alternative name for the study drug gabapentin enacarbil; a drug substance code used by Astellas Pharma Inc.
GSK1838262	Alternative name for the study drug gabapentin enacarbil; a drug substance code used by GlaxoSmithKline K.K.
XP13512	Alternative name for the study drug gabapentin enacarbil; a Drug substance code used by XenoPort, Inc.

IV SYNOPSIS

Date and Version No of Protocol Synopsis: Version 3.0, dated 13 January 2017	
Sponsor: Astellas Pharma Inc.(API)	**Protocol Number:** 8825-CL-0101
Name of Study Drug: Gabapentin enacarbil	**Phase of Development:** Post-marketing clinical study
Title of Study: Gabapentin enacarbil post-marketing clinical study - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study in Subjects With Restless Legs Syndrome -	
Planned Study Period: December 2016 to November 2018	
Study Objectives: - To verify the efficacy of oral gabapentin enacarbil 600 mg once daily compared with placebo on the basis of the change from baseline in IRLS score in patients with moderate to severe idiopathic restless legs syndrome (RLS), using a multicenter, randomized, double-blind, parallel-group, comparative design - To evaluate the safety of gabapentin enacarbil 600 mg	
Planned Total Number of Study Centers and Location: Approximately 50 centers Japan	
Study Population: Patients with moderate to severe idiopathic RLS	
Number of Subjects to be Enrolled/Randomized: 360 subjects as participants in the treatment period (180 subjects per group × 2)	
Study Design Overview: Gabapentin enacarbil 600 mg or placebo will be administered orally once daily after the evening meal. Patients meeting the inclusion and exclusion criteria at provisional registration will receive single-blind placebo for 1 week (run-in period). Of these, patients meeting the inclusion and exclusion criteria at formal registration will be randomized to recieve double-blind treatment with either gabapentin enacarbil 600 mg or placebo for 12 weeks (treatment period). After the end of the 12-week treatment period, single-blind placebo will be given for 1 week (follow-up period) for follow-up observation. However, of the patients meeting the inclusion and exclusion criteria at formal registration, those with an estimated creatinine clearance of ≥ 60 to < 90 mL/min at the start of the run-in period will receive randomized double-blind treatment initially with either gabapentin enacarbil 300 mg or placebo for 1 week (upward titration period) followed by gabapentin enacarbil 600 mg or placebo for 11 weeks, totaling 12 weeks (treatment period including the upward titration period). [Randomiation method] Stratified allocation will be performed with stratification factors of age (< 50 years and ≥ 50 years) at the start of the run-in period and estimated creatinine clearance (≥ 60 to < 90 mL/min and ≥ 90 mL/min) at the start of the run-in period.	
Inclusion/Exclusion Criteria:	

Inclusion:
Subject is eligible for the study if all of the following apply:
At provisional registration:

1. Provided written informed consent using the informed consent form approved by the Institutional Review Board (IRB) prior to any study-related procedures (including discontinuation of excluded concomitant medications)
2. Male or female outpatient aged between ≥ 20 and ≤ 80 years years at the time of consent
3. Patient with a diagnosis of RLS according to the International RLS Study Group diagnostic criteria for RLS (2014 update)
4. Had RLS symtoms for ≥ 15 days during the month prior to the start of the run-in period, or if on treatment for RLS, during the month prior to the start of that treatment
5. Has an International Restless Legs Syndrome Rating Scale (IRLS) score of ≥ 15 at the start of the run-in period
6. Has not taken dopamine agonists, dopamine preparations, gabapentin, gabapentin enacarbil, or pregabalin during at least one week before the first day of the run-in period
7. Has not received other treatments for RLS (opioids, benzodiazepines, long-acting dopamine agonists) during at least 2 weeks before the first day of the run-in period
8. Female subject must either:
   Be of nonchildbearing potential:
   - Postmenopausal (defined as at least 1 year without any menses) at the start of the run-in period, or
   - Documented surgically sterile

   Or, if of childbearing potential,
   - Agree not to become pregnant during the study and for 28 days after the final study drug administration,
   - And have a negative pregnancy test at the start of the run-in period
   - And if heterosexually active, agree to consistently use two (one or both of which must be the barrier method) of the established forms of birth control* specified below, during the study period and for 28 days after the final study drug administration
     *Established forms of birth control include:
     - Correct usage of approved oral contraceptives
     - Intrauterine device (IUD), intrauterine system (IUS), and other intrauterine instruments
     - Barrier method with male condoms or female condoms
     - Rhythm method (Knaus-Ogino method)
9. Female subject must agree not to breastfeed throughout the study period and for 28 days after the final study drug administration.
10. Female subject must not donate ova throughout the study period and for 28 days after the final study drug administration.
11. Agrees not to participate in another interventional study during the study period
12. Has a body mass index (BMI) range of 18.5 to < 30 (BMI = Body weight (kg)/Height $(m)^2$)

At formal registration:

13. Has an IRLS score of ≥ 15 at the start of the treatment period
14. Has RLS symtoms (evenings and nights) for at least 4 days during the 1-week run-in period
15. Has an estimated creatinine clearance value* of ≥ 60 mL/min as calculated using the Cockcroft-Gault equation at the start of the run-in period
    *For calculation of the estimated creatinine clearance, refer to ***Section 5.7 Other Measurements, Assessments or Methods***.

Waivers to the inclusion criteria will **NOT** be allowed.

Exclusion:
Subject will be excluded from participation if any of the following apply:

At provisional registration:

1. A sleep disorder (e.g., sleep apnea) that may affect the assessment of RLS
2. A history of RLS symptom augmentation or post-therapy rebound with previous dopamine agonist treatment
3. Neurologic disease or movement disorder (e.g., neurologic disease, Parkinson's disease, multiple sclerosis, dyskinesia, dystonia, rheumatoid arthritis)
4. Poorly controlled diabetes mellitus (i.e., HbA1c > 7.5% [NGSP-value] on a test during the past 6 months), iron deficiency anemia, or current use of oral sedative-hypnotics
5. Has a history of suicide attempt within 6 months before consent, or judged by the investigator/sub-investigator to be at risk for suicide
6. Has elevated ALT or AST (based on laboratory data within the past 6 months) (For reference, grade ≥ 2 according to the "Criteria for Seriousness/Severiy Grading of Adverse Drug Reactions," [Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, dated June 29, 1992] will be used.)
7. Moderate or severe depression (DSM-V)
8. Previously had alcohol dependence or drug poisoning, or within the past year had substance abuse or dependence.
9. Shift worker (including night-work), professional driver, or dangerous machinery operater
10. Clinically significant or unstable medical conditions (e.g., current or past history of cancer, complication of serious cardiac disease*, hepatic disease*, renal disease*, hematological disease*, immunodeficiency, psychiatric disease).
    *For reference, Grade 3 of the "Criteria for Seriousness/Severiy Grading of Adverse Drug Reactions," (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, dated June 29, 1992) will be used.
11. History of hypersensitivity to gabapentin
12. Had previously taken pregabalin, gabapentin enacarbil, or ASP8825 (including GSK1838262 and XP13512) as an investigational drug
13. Participated within 12 weeks (84 days) before the first day of the run-in period, or currently participating, in a clinical trial or post-marketing clinical study of another drug or a medical device
14. Is employed by the Sponsor or the CRO, SMO or study site involved in this study
15. Other subjects for whom participation in this study is judged to be inappropriate in the opinion of the investigator/sub-investigator

At formal registration:

16. Has a decrease in IRLS score at the start of the treatment period by 10 or more points from the start of the run-in period
17. Has clinically relevant abnormalities on laboratory tests* in the opinion of the investigator/sub-investigator
    *For reference, Grade 3 of the "Criteria for Seriousness/Severiy Grading of Adverse Drug Reactions," (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, dated June 29, 1992) will be used.
18. Poorly controlled diabetes mellitus (i.e., HbA1c > 7.5% [NGSP-value] on a laboratory test in the run-in period)
19. Serum ferritin < 12 ng/mL on a laboratory test at the start of the run-in period
20. Elevated ALT or AST on laboratory tests at the start of the run-in period (For reference, grade ≥ 2 according to the "Criteria for Seriousness/Severiy Grading of Adverse Drug Reactions," [Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, dated June 29, 1992] will be used.)
21. Female other than female of nonchildbearing potential judged to be pregnant based on the pregnancy test in the run-in period (in line with inclusion criterion 8)
22. Subjects for whom participation in this study is judged to be inappropriate in the opinion of the investigator/sub-investigator

Waivers to the exclusion criteria will **NOT** be allowed.

Test Drug:
Gabapentin enacarbil tablets 300 mg

Dose:
Gabapentin enacarbil 600 mg group: 600 mg/day of gabapentin enacarbil

Mode of Administration:
Orally once daily after the evening meal

Treatment group	Run-in period (1 week)	Treatment period (12 weeks)		Follow-up period (1 week)
		Upward titration period (1 week)	(11 weeks)	
Placebo group (0 mg/day)	○○	○○	○○	○○
600 mg group (600 mg/day) (Subjects with an estimated creatinine clearance of ≥ 90 mL/min at the start of the run-in period)		●●	●●	
600 mg group (600 mg/day) (Subjects with an estimated creatinine clearance of ≥ 60 to < 90 mL/min at the start of the run-in period)		○●	●●	

●: Gabapentin enacarbil tablets 300 mg. ○: Placebo matching gabapentin enacarbil tablets.

Comparative Drug:
Placebo matching gabapentin enacarbil tablets

Dose:
Placebo group: 0 mg/day of gabapentin enacarbil

Mode of Administration:
See the "Test Drug" section.

Concomitant Medication Restrictions or Requirements:
Excluded concomitant medications

1. Concomitant use of the following drugs will be prohibited from 14 days before the first day of the run-in period through the end of the study period:
   - Benzodiazepines (for only if used to treat RLS): clonazepam, etc.
   - Opioids: codeine, oxycodone, morphine, etc.
   - Long-acting dopamine agonists: cabergoline, etc.
2. Concomitant use of the following drugs will be prohibited from 7 days before the first day of the run-in period through the end of the study period:
   - Dopamine agonists: pramipexole (BI-Sifrol®), talipexole, rotigotine (Neupro Patch®), ropinirole, etc.
   - Dopamine preparations: levodopa/carbidopa combined drug, etc.
   - Gabapentin: Gabapen®
   - Gabapentin enacarbil: Regnite®
   - Pregabalin: Lyrica®
3. Concomitant use of the following drugs will be prohibited from the first day of the run-in period through the end of the study period:
   - Dopamine receptor inhibitors: Primperan (metoclopramide), Nauzelin (domperidone), etc.

- Central depressants (hypnotics, antianxiety drugs, antipsychotic druga, antidepressants, antimanic drugs, antiepileptic drugs)
- Magnesium preprations[*1], iron preparations[*1], folic acid[*1], vitamin B12 preparations[*1]
- Other investigational products or post-marketing clinical studys

[*1] These apply to prescription drugs

4. The following drugs are prohibited for concomitant use from 7 days before a visit (day of IRLS score assessment) until the time of the IRLS score assessment at the visit, between the first day of the run-in period and the end of the study period:
   - Antihistamines

Duration of treatment:
See the "Test Drug" section.

Discontinuation Criteria

1. Adverse events (AEs)
   - Subject experiences an AE, and further participation in the study is judged to be difficult.
2. Lack of efficacy (Worsening of the target disease)
   - Subject has insufficient improvement with the study drug, and is judged to require change of treatment.
   - Subject has worsening of the target disease, and further participation in the study is judged to be difficult.
3. Withdrawal of consent
   - Subject requests to withdraw from the study.
4. Lost to follow-up
   - Subject changed residence or is referred to another clinic/hospital or has other personal reasons such as busy schedule, which prevents further participation in the study.
   - Subject does not return to the study site (or lost contact with the study site).
5. Ineligibility (i.e., not fulfilling the inclusion criteria or meeting any of the exclusion criteria)
   - Subject is noted not to fulfill the inclusion criteria or to meet any of the exclusion criteria, on the basis of the results of tests or observations performed after the informed consent and before formal registration.
6. Protocol deviation
   - Subject is found not to have met the inclusion/exclusion criteria, after formal registration as an eligible subject.
   - Subject is found to have any other major deviation from the protocol.
7. Suicide
   - Subject attempted suicide, or is judged by the investigator/sub-investigator to be at high risk for suicide.
8. Death
   - Subject died (from any cause).
9. Pregnancy
   - Female subject is found to be pregnant during the study period.
10. Other
    - The investigator/sub-investigator judges that further study treatment is inappropriate

in the subject, or the Sponsor requests to discontinue study treatment in the subject because of safety issues.
Endpoints for Evaluation: Efficacy Endpoints **Primary:** • Change from baseline in IRLS score at the end of treatment period (Week 12) **Secondary:** • Change from baseline in IRLS score at each time point • Investigator-rated Clinical Global Impression (ICGI) responder rate • Patient-rated Clinical Global Impression (PCGI) responder rate • Change from baseline in Pittsburgh Sleep Quality Index • Change from baseline in Athens Insomnia Scale • Change from baseline in RLS Pain score • Change from baseline in EQ-5D-5L Safety endpoints • Vital signs • Adverse events • Laboratory tests • Body weight • Epworth Sleepiness Scale
Statistical Methods: **Sample size justification:** On the basis of Japanese phase II/III study [CL-0003] results, the difference between treatment groups in the primary endpoint of this study, i.e., the change from baseline in IRLS score at the end of treatment period (Week 12), was assumed to be −2.56, with a standard deviation of 8.000 in both groups. Under these assumptions, to detect a statistically significant difference between gabapentin enacarbil and placebo using a 2-sample t-test with a two-sided significance level of 0.05 and a power of 80%, 155 subjects per group would be required. Assuming the discontinuation rate during the treatment period was approximately 15.0% in each group, the sample size has been set to 180 per group.

Efficacy:
The primary analysis set will be FAS (which will consist of all subjects who received the study drug for the reatment period and were evaluated for at least one efficacy endpoint during the treatment period).

< Anlaysis of the primary efficacy endpoint >
The primary efficacy endpoint is the change from baseline in IRLS score at the end of treatment period. Using a repeated measures analysis of variance model having the following average structure, the adjusted mean in each treatment group and its difference (gabapentin enacarbil group − placebo group) at the end of treatment period (Week 12) will be calculated, with comparison between the placebo group and the gabapentin enacarbil group:

Change in IRLS score at each time point
= IRLS score at baseline + Age category*[1)] + Estimated creatinine clearance category *[2)] + Treatment group + Time point + Treatment group × Time point
[*1)]Age category: < 50 years and ≥ 50 years
[*2)]Estimated creatinine clearance category: ≥ 60 to < 90 mL/min and ≥ 90 mL/min

Compound symmetry will be used as the covariance structure for repeated measures of the response variable. A two-sided significance level of 0.05 will be used for statistical tests.

Pharmacokinetics:
No pharmacokinetic evaluation will be performed.

Pharmacodynamics:
No pharmacodynamic evaluation will be performed.

Safety:
Using safety analysis set, the following analyses will be performed by treatment group:

- Adverse events

The frequency of AEs will be tabulated. In addition, AEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) of the the Medical Dictionary for Regulatory Activities (MedDRA).

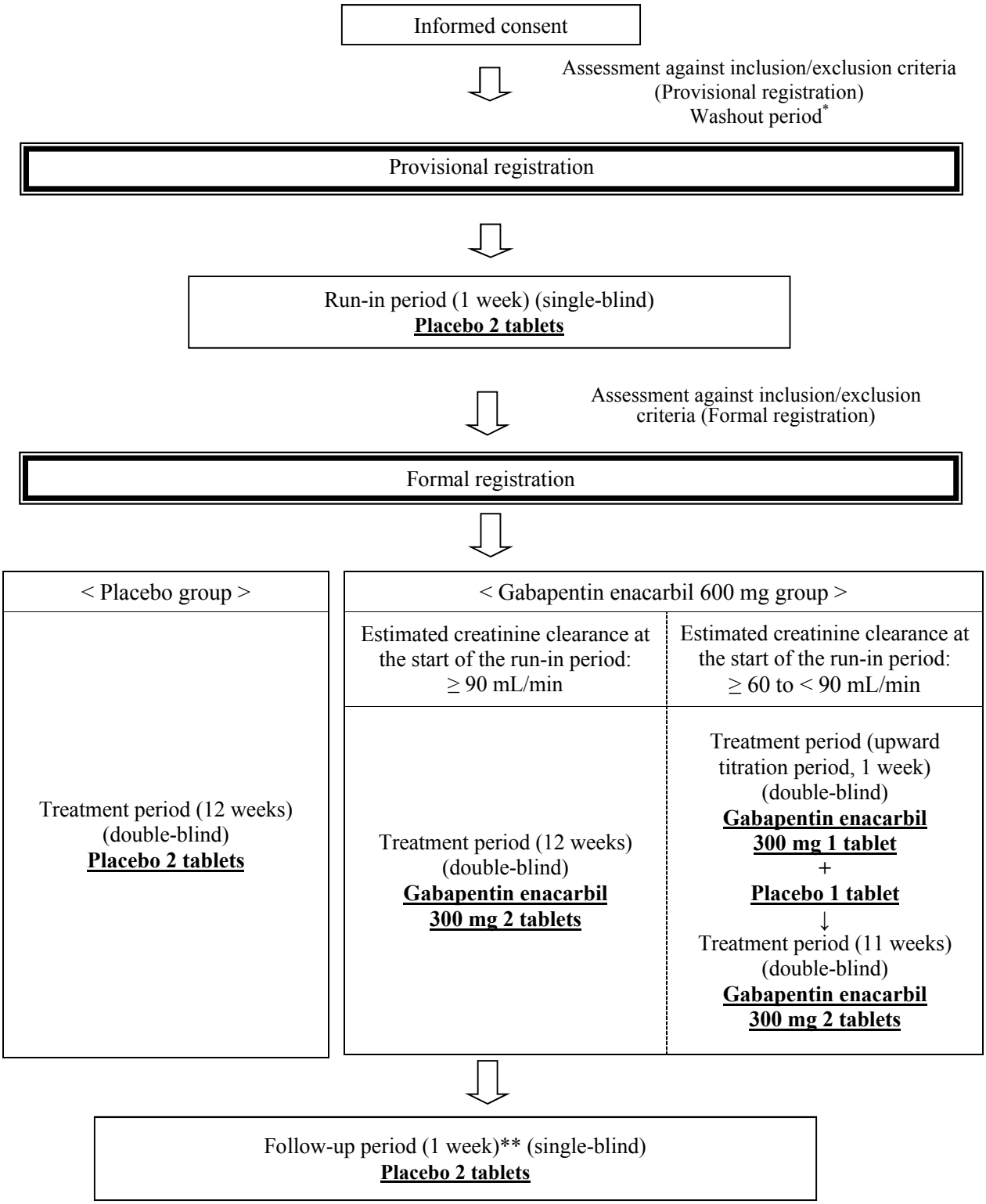
- Vital signs, laboratory test values, body weight, and Epworth Sleepiness Scale

The measured value and its change from baseline at each time point will be summarized using descriptive statistics. The frequency will be tabulated as needed.

Interim analysis:
Not applicable.

V FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



* Subjects using the following drugs before the start of the run-in period will require the specified washout period:
1. Dopamine agonists, dopamine preparations, gabapentin, pregabalin: ≥ 7 days
2. Opioids, benzodiazepines (for only if used to treat RLS), long-acting dopamine agonists: ≥ 14 days

** For the subjects discontinued during the treatment period, the tests/observations required at discontinuation will be performed and then post-treatment follow-up will be performed as far as possible, but this does not require the use of placebo during the follow-up period.

< Start and end of the post-marketing clinical study >

The time of the start of this post-marketing clinical study is defined as the time at which informed consent is obtained from the first subject. The time of the end of this post-marketing clinical study is defined as the time at which protocol-specified final assessment is implemented in the last subject.

Table 1: Schedule of Assessments

	Run-in period	Treatment period								Follow-up period	Discontinuation[*5]
	W-1	W0	W1	W2	W4	W6	W8	W10	W12	W13	
Day of observation	−7	1	8	15	29	43	57	71	85	Last dosing of the study drug for the treatment period + 8 days[*4]	
Allowed visit window	−10 to −7	1	5 to 11	12 to 18	26 to 32	40 to 46	54 to 60	68 to 74	82 to 88	Last dosing of the study drug for the treatment period + 5 to 11 days[*4]	
Visit	●	●	●	●	●	●	●	●	●	●	●
Informed consent	●										
Subject characteristics	●										
Assessment against inclusion/ exclusion criteria	●	●									
Patient registration	● Provisional	● Formal									● Discontinuation
Prescription of the study drug	●	●	●[*3]	●	●	●	●	●	●		
Compliance status		●	●	●	●	●	●	●	●	●	●
Concomitant medication monitoring	●	●	●	●	●	●	●	●	●	●	●
IRLS score	●	●	●	●	●	●	●	●	●	●	●
ICGI			●	●	●		●		●	●	●
PCGI			●	●	●		●		●	●	●
Pittsburgh Sleep Quality Index		●			●		●		●		●
Athens Insomnia Scale		●			●		●		●		●
EQ-5D-5L		●			●		●		●		●
RLS Pain score	●	●	●	●	●	●	●	●	●	●	●
Epworth Sleepiness Scale		●	●	●	●	●	●	●	●	●	●
Laboratory tests	◎	◎		◎	◎		◎		◎		◎
Thyroid function tests (TSH, Free T_4)		◎							◎		◎
HbA1c	◎										
Ferritin	◎										
Estimated creatinine clearance	●										
Pregnancy test[*1]	●								●		●
Height	●										
Body weight	●	●			●		●		●		●
Vital signs	●	●	●	●	●	●	●	●	●		●
Adverse event monitoring[*2]	●	●	●[*3]	●	●	●	●	●	●	●	●

◎Central measurements

*[1] Not required in men, postmenopausal women (no menstruation for at least 1 year), or other women with a history of hysterectomy, bilateral oophorectomy, etc. in whom a possibility of pregnancy is clearly excluded.

*[2] A medical interview should determine any occurrence of eye disorders such as blurred vision or accommodation disorder.

*[3] In subjects with an estimated creatinine clearance of ≥ 60 to < 90 mL/min at the start of the run-in period randomized to the gabapentin enacarbil group, in whom the dose is titrated from 300 mg to 600 mg, any occurrence of AEs should be carefully assessed and the subject's condition should be adequately observed, based on which whether the subject can continue with the study should be carefully determined.

*[4] Follow-up observation will occur on the day of "last dosing of the study drug for the treatment period +8 days," which will be Day 92 in subjects who take the study drug for the treatment period up to Day 84 per protocol.

*[5] For the subjects discontinued during the run-in period, the compliance status and any AEs will be investigated.

For the subjects discontinued during the treatment period, the tests/observations required at discontinuation will be performed, and then post-treatment follow-up (i.e., the Week 13 procedure) will be performed as far as possible, but this does not require the use of placebo during the follow-up period.

For the subjects discontinued during the follow-up period, the Week 13 procedure will be performed as the tests/observations at discontinuation.

1 INTRODUCTION

1.1 Background

Restless legs syndrome (RLS) is believed to be caused by a central nervous system disorder, and manifests as an overwhelming urge to move the legs, usually due to uncomfortable sensations in the limbs (primarily in the legs). Associated symptoms include unusual sensations that can vary among patients, such as periodic limb movements or involuntary movements during sleep, hot flashes, or pain. Because of nocturnal worsening of the urge to move the legs and uncomfortable unusual sensations, with resultant disturbance of sleep initiation and maintenance, many patients complain of chronic fatigue or insomnia. RLS is thus classified as a sleep abnormality in the International Classification of Sleep Disorders, established in 1990 mainly by the American Sleep Disorders Association. Also in Japan, RLS is handled as a sleep disorder in the Guidelines for Measures and Treatment for Sleep Disorders, established in 2002.

The prevalence of RLS in the U.S. and Europe, where RLS is a common sensorimotor disorder, has been reported to be 5.5%–11.6% of the population [Rinaldi et al., 2016]. In Japan, the reported prevalence of RLS is 1.0%–4.0%, which is lower than that in the Western countries and similar to that in other Asian countries [Nomura et al., 2012]. Despite increasing recognition of this disease year by year owing to public enlightenment through media such as television and newspapers, the proportion of patients who visited medical institutions and are treated remains limited.

In the Treatment Algorithm for RLS published in 2004 by the Restless Legs Syndrome Foundation in the U.S., RLS was classified into intermittent, daily, and refractory types, with recommendations on pharmacological therapies appropriate for the symptoms and conditions of each type [Silber et al., 2004]. In the 2013 update version of the algorithm, non-pharmacologic approaches to prevent exacerbation were introduced, while treatment with a non-ergot dopamine agonist or a calcium channel $\alpha_2\delta$ receptor ligand is recommended for daily RLS [Rinaldi et al., 2016; Silber et al., 2013].

Gabapentin is an $\alpha_2\delta$ receptor ligand created by Pfizer, Inc. in the U.S. In Japan, gabapentin was approved in July 2006 for marketing with the indication of "adjunctive therapy for the treatment of partial seizures with and without secondary generalization in patients with epilepsy that did not sufficiently respond to other antiepileptic agents." While various reports described the pharmacokinetics of gabapentin, marked variability in absorption following oral administration is well known [Gidal et al., 2000; Boyd et al., 1999; Gidal et al., 1998; Beydoun et al., 1995]. Another known drawback of gabapentin is that, despite an established dose-dependent effect with oral administration, the drug absorption is saturated around the clinical dose because of saturation of transporters responsible for the absorption, and thus some patients do not have expected clinical response even with a dose increase. On the other hand, off-label use of gabapentin for RLS in overseas clinical studies demonstrated therapeutic effects [Garcia-Borreguero et al., 2002; Happe et al., 2001; Thorp et al., 2001; Adler, 1997; Mellick et al., 1996]. Gabapentin is positioned as one of the first-line agents

along with dopamine agonists in the RLS Treatment Algorithm as stated above [Rinaldi et al., 2016; Silber et al., 2013].

Gabapentin enacarbil is a new prodrug of gabapentin with improved absorption, created by XenoPort, Inc. in the U.S. to overcome the pharmacokinetic drawbacks of gabapentin. Gabapentin enacarbil is designed to be stable in the gastrointestinal tract, actively absorbed by the high-capacity transport mechanisms present throughout the intestine, and rapidly converted to gabapentin in the body by hydrolysis. The blood concentrations of gabapentin following the oral administration of gabapentin enacarbil have been demonstrated to be dose-dependent. In summary of the above, gabapentin enacarbil, a prodrug of gabapentin, has improved pharmacokinetics and thus is expected to exert stable clinical efficacy, and is currently positioned as one of the first-line agents in the RLS treatment algorithm [Rinaldi et al., 2016; Silber et al., 2013].

In Japan, the new drug approval application for gabapentin enacarbil was filed in 19 November 2009. Subsequently, on 02 December 2011, the First Committee on Drugs concluded that Regnite Tablets 300 mg may be approved (Dosage and Administration: The usual adult dose for oral use is 600 mg as gabapentin enacarbil once daily after dinner). However, the efficacy of gabapentin enacarbil 600 mg was not verified by the primary analysis of the Japanese phase II/III study [CL-0003], and "implementation of a clinical study to verify the efficacy of gabapentin enacarbil 600 mg" was included in the advice based on the deliberation results of the First Committee on Drugs. Thus, this post-marketing clinical study has been planned to verify the efficacy of gabapentin enacarbil 600 mg.

1.2 Nonclinical and Clinical Data

1.2.1 Nonclinical Data

Gabapentin enacarbil is a prodrug of gabapentin, and is converted to gabapentin in the body rapidly after absorption following oral administration. Although no detailed mechanism of the action of gabapentin in the treatment of RLS has been elucidated, a suggested contributing mechanism is that gabapentin binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels [Marais et al., 2001], thereby preventing presynaptic influx of calcium ions, which results in a reduction in the release of excitatory neurotransmitters [Fink et al., 2000].

There have been no established animal models appropriately reflecting the disease condition of RLS, and thus no pharmacological studies to support the efficacy of gabapentin enacarbil have been conducted. However, since gabapentin enacarbil is rapidly hydrolyzed to gabapentin in the body, the maximum blood concentration of the unchanged drug in humans is very low, compared to that of gabapentin. In addition, given that gabapentin enacarbil does not bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, unlike gabapentin, and has very low affinity for dopamine and other receptors, ion channels, and transporters, the therapeutic efficacy of gabapentin enacarbil is exerted based on gabapentin produced in the living body [Kaneko, 2012].

Gabapentin has been reported to improve excessive signal transmission by the following mechanisms [Kaneko, 2012]:

1. It binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels in the excitatory nerve ending, and suppresses the release of excitatory neurotransmitters (e.g., glutamate).
2. It increases the amount of GABA in the brain and activates GABA transporters, thereby promoting intracellular uptake of GABA, leading to activation of GABA neurons.

1.2.2 Clinical Data

1) Japanese phase II/III study [CL-0003]

This was a placebo-controlled, randomized, double-blind, parallel-group, comparative study to evaluate the efficacy, safety, and pharmacokinetics of gabapentin enacarbil in Japanese patients (target sample size, 400 patients; 100 patients per group) with RLS diagnosed according to the diagnostic criteria established by the International RLS Study Group.

As for the dosage regimen, during the run-in period placebo was to be administered in a single-blind manner orally for 1 week, and during the treatment period gabapentin enacarbil 600, 900, 1200 mg or placebo was to be administered orally after evening meals. In the gabapentin enacarbil group, the starting dose was 600 mg, and 3 days later the dose was increased to 600, 900 or 1200 mg (or unchanged in the 600 mg group), with the duration of treatment set to 12 weeks.

All of the 469 treated subjects (116 subjects in the placebo group, 120 subjects in the 600 mg group, 119 subjects in the 900 mg group, 114 subjects in the 1200 mg group) were included in the safety analysis set. Of these, after 1 subject with missing efficacy endpoint data was excluded, the remaining 468 subjects (116 subjects in the placebo group, 120 subjects in the 600 mg group, 119 subjects in the 900 mg group, 113 subjects in the 1200 mg group) were included in the FAS and analyzed for efficacy.

The change from baseline in IRLS score [International Restless Legs Syndrome Study Group, 2003] at final evaluation in the FAS, which was the primary endpoint of the study, is shown in Table 2. Compared with the placebo group, the 1200 mg group showed a statistically significant difference ($P = 0.011$, Williams' multiple comparison test). On the other hand, the 900 mg group and the 600 mg group did not show superiority to the placebo group.

Table 2: Change in IRLS score at final observation in the treatment period: FAS

Variable	Treatment group	N	Mean	Standard deviation	Gabapentin enacarbil group-Placebo group	95% confidence interval for Gabapentin enacarbil group-Placebo group	Statistical test†
IRLS score	Placebo	116	−8.96	7.286	-	-	-
	600 mg	120	−11.10	7.921	−2.14	−4.097 to −0.189	-‡
	900 mg	119	−10.28	7.750	−1.32	−3.255 to 0.614	P = 0.052
	1200 mg	113	−11.38	8.297	−2.42	−4.455 to −0.392	P = 0.011

†Williams' multiple comparison test (lower limit) [significance level: one-sided, 0.025]

‡ Not applicable for Williams' multiple comparison test

Table 3 summarizes the Investigator-rated Clinical Global Impression (ICGI) and Patient-rated Clinical Global Impression (PCGI) results at final observation in the treatment period from baseline. Subjects who were "Very much improved" or "Much improved" were defined as "Responders," and others were defined as "Non-responders." The proportion of responders was defined as the responder rate.

The ICGI responder rate at final observation in the treatment period was 44.8% in the placebo group, 65.8% in the 600 mg group, 52.9% in the 900 mg group, and 62.8% in the 1200 mg group, showing superiority of all gabapentin enacarbil groups to the placebo group ($P < 0.001$ for the 600 mg group, $P = 0.014$ for the 900 mg group, $P = 0.003$ for the 1200 mg group). In addition, the PCGI responder rate at final observation in the treatment period was 44.0% in the placebo group, 65.8% in the 600 mg group, 52.1% in the 900 mg group, and 61.9% in the 1200 mg group, showing superiority of all gabapentin enacarbil groups to the placebo group ($P < 0.001$ for the 600 mg group, $P = 0.012$ for the 900 mg group, $P = 0.003$ for the 1200 mg group).

Table 3: ICGI and PCGI at final observation in the treatment period: FAS

Variable	Treatment group	N	Responders	Response rate	95% confidence interval for the response rate	Difference in the responder rate		Statistical test†
						Gabapentin enacarbil group-Placebo group	95% confidence interval for Gabapentin Enacarbil group-Placebo group	
ICGI	Placebo	116	52	44.8%	35.59 to 54.34	-	-	-
	600 mg	120	79	65.8%	56.62 to 74.24	21.01	8.60 to 33.41	P < 0.001
	900 mg	119	63	52.9%	43.58 to 62.15	8.11	−4.63 to 20.85	P = 0.014
	1200 mg	113	71	62.8%	53.24 to 71.74	18.00	5.30 to 30.70	P = 0.003
	Total	468	265	56.6%	52.00 to 61.17	-	-	-
PCGI	Placebo	116	51	44.0%	34.76 to 53.48	-	-	-
	600 mg	120	79	65.8%	56.62 to 74.24	21.87	9.47 to 34.26	P < 0.001
	900 mg	119	62	52.1%	42.75 to 61.34	8.14	−4.60 to 20.87	P = 0.012
	1200 mg	113	70	61.9%	52.33 to 70.92	17.98	5.26 to 30.70	P = 0.003
	Total	468	262	56.0%	51.35 to 60.54	-	-	-

†Shirley-Williams' multiple comparison test (upper limit) [significance level: one-sided, 0.025]

AEs (including abnormal laboratory test values) were reported in 71.6% (83/116 subjects) in the placebo group, 76.7% (92/120 subjects) in the 600 mg group, 84.0% (100/119 subjects) in the 900 mg group, and 85.1% (97/114 subjects) in the 1200 mg group. There were no deaths or other serious adverse events (SAEs).

AEs (including abnormal laboratory test values) for which a causal relationship to the study drug was not ruled out were reported in 50.9% (59/116 subjects) in the placebo group, 56.7% (68/120 subjects) in the 600 mg group, 69.7% (83/119 subjects) in the 900 mg group, and 72.8% (83/114 subjects) in the 1200 mg group. Common events included dizziness (8 subjects in the placebo group, 30 subjects in the 600 mg group, 30 subjects in the 900 mg group, and 33 subjects in the 1200 mg group), somnolence (19 subjects in the placebo group, 23 subjects in the 600 mg group, 32 subjects in the 900 mg group, and 37 subjects in the 1200 mg group), headache (6 subjects in the placebo group, 5 subjects in the 600 mg group, 9 subjects in the 900 mg group, and 5 subjects in the 1200 mg group), nausea (0 subjects in the placebo group, 6 subjects in the 600 mg group, 5 subjects in the 900 mg group, and 4 subjects in the 1200 mg group).

Vital signs (blood pressure and pulse rate) showed no clinically relevant changes.

As electrocardiogram (ECG)-related AEs, aortic dilatation and arrhythmia (each in 1 subject) were reported in 2 subjects in the 600 mg group.

In summary of the above, the study demonstrated the superiority of gabapentin enacarbil 1200 mg to placebo in Japanese patients with RLS, and did not raise any major concerns about the safety of gabapentin enacarbil up to 1200 mg.

2) Overseas phase III study [XP052]

This was a placebo-controlled, randomized, double-blind, parallel-group, comparative study to evaluate the efficacy and safety of gabapentin enacarbil in non-Japanese patients (target sample size 210 subjects; 105 subjects per group) with RLS diagnosed according to the diagnostic criteria established by the International RLS Study Group.

As for the dosage regimen, gabapentin enacarbil 1200 mg or placebo was administered orally once daily at 17:00 with a meal (in the gabapentin enacarbil group, the starting dose was 600 mg, and 3 days later the dose was increased to 1200 mg), with the duration of treatment set to 12 weeks.

All of the 221 treated subjects (108 subjects in the placebo group, 113 subjects in the gabapentin enacarbil group) were included in the safety analysis set. Of these, after 1 subject without efficacy evaluation was excluded, the remaining 220 subjects (108 subjects in the placebo group, 112 subjects in the gabapentin enacarbil group) were included in the MITT analysis set and analyzed for efficacy.

The change from baseline in IRLS score at final evaluation in the MITT analysis set, which was a primary endpoint of the study, is shown in Table 4. A paired comparison between the placebo group and the gabapentin enacarbil group showed a statistically significant difference (P = 0.0003; analysis of covariance adjusted for pooled study site and baseline).

Table 4: Change from baseline in IRLS score at Week 12 using LOCF (MITT analysis set)

	Placebo n = 108	**XP13512* n = 112**	**Mean difference (XP13512 group − placebo group)**	**95% CI**
	Mean (SD)	**Mean (SD)**		
Baseline	22.6 (4.91)	23.1 (4.86)		
Week 12	13.8 (7.47)	9.8 (8.70)		
Change from baseline	−8.8 (8.63)	−13.2 (9.21)	−4.0	−6.2, −1.9

*Gabapentin enacarbil

The ICGI responder rate at final evaluation, which was another primary endpoint of the study, was 38.9% (42/108 subjects) in the placebo group and 76.1% (83/109 subjects) in the gabapentin enacarbil group with an odds ratio [95% confidence interval] of 5.1 [2.8, 9.2], showing a statistically significant difference between the placebo group and the gabapentin enacarbil group (P < 0.0001; logistic regression analysis model with treatment group and pooled study site as explanatory variables).

AEs (including abnormal laboratory test values) were reported in 74.1% (80/108 subjects) in the placebo group and 82.3% (93/113 subjects) in the gabapentin enacarbil group. There were no deaths. An SAE other than deaths was reported in 1 subject in the placebo group (appendicitis), for which a causal relationship to the study drug was ruled out.

AEs for which a causal relationship to the study drug was not ruled out were reported in 40.7% (44/108 subjects) in the placebo group and 70.8% (80/113 subjects) in the gabapentin enacarbil group. Common events included somnolence (8 subjects in the placebo group, 29 subjects in the gabapentin enacarbil group), dizziness (3 subjects in the placebo group, 20 subjects in the gabapentin enacarbil group), headache (8 subjects in the placebo group, 14 subjects in the gabapentin enacarbil group), fatigue (2 subjects in the placebo group, 11 subjects in the gabapentin enacarbil group), and nausea (2 subjects in the placebo group, 9 subjects in the gabapentin enacarbil group).

As an AE related to vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), orthostatic hypotension was reported in 1 subject in the gabapentin enacarbil group.

ECG showed no clinically relevant abnormal findings.

In summary of the above, the study demonstrated the efficacy of gabapentin enacarbil 1200 mg for 12 weeks in non-Japanese patients with RLS, and raised no particular major concerns about the safety.

3) Overseas phase III study [XP053]

This was a placebo-controlled, randomized, double-blind, parallel-group, comparative study to evaluate the efficacy and safety of gabapentin enacarbil in non-Japanese patients (target sample size 315 subjects; 105 subjects per group) with RLS diagnosed according to the diagnostic criteria established by the International RLS Study Group.

As for the dosage regimen, gabapentin enacarbil 600 or 1200 mg or placebo was administered orally once daily at 17:00 with a meal (in the 1200 mg group, the starting dose was 600 mg, and 3 days later the dose was increased to 1200 mg), with the duration of treatment set to 12 weeks.

All of the 322 treated subjects (96 subjects in the placebo group, 115 subjects in the 600 mg group, and 111 subjects in the 1200 mg group) were included in the safety analysis set. Of these, after 1 subject without efficacy evaluation, the remaining 321 subjects (96 subjects in the placebo group, 114 subjects in the 600 mg group, and 111 subjects in the 1200 mg group) were included in the MITT analysis set and analyzed for efficacy.

The change from baseline in IRLS score at final evaluation in the MITT analysis set, which was a primary endpoint of the study, is shown in Table 5. The gabapentin enacarbil 1200 mg group showed a statistically significant difference compared with the placebo group (P = 0.0015; analysis of covariance adjusted for study site and baseline).

Table 5: Change from baseline in IRLS score at Week 12 using LOCF (MITT analysis set)

	Placebo n = 96		**XP13512 1200 mg n = 111**		**Mean difference[1)]**	**95% CI**
	Mean	**SD**	**Mean**	**SD**		
Baseline	23.8	4.58	23.2	5.32		
Week 12	14.0	7.87	10.2	8.03		
Change from baseline	−9.8	7.69	−13.0	9.12	−3.5	−5.6, −1.3

[1)] Calculated as "XP13512 1200 mg group − Placebo group"

The ICGI responder rate at final evaluation, which was another primary endpoint of the study, was 44.8% (43/96 subjects) in the placebo group and 77.5% (86/111 subjects) in the 1200 mg group with an odds ratio [95% confidence interval] of 4.3 [2.3, 7.9], showing a statistically significant difference between the placebo group and the gabapentin enacarbil 1200 mg group

($p < 0.0001$; logistic regression model with treatment group and pooled study site as explanatory variables).

AEs (including abnormal laboratory test values) were reported in 79.2% (76/96 subjects) in the placebo group, 87.0% (100/115 subjects) in the 600 mg group, and 84.7% (94/111 subjects) in the 1200 mg group. There were no deaths. Other SAEs were reported in 1 subject in the placebo group (cholelithiasis) and 2 subjects in the 600 mg group (cellulitis and intervertebral disc protrusion, each in 1 subject), for all of which a causal relationship to the study drug was ruled out.

AEs (including abnormal laboratory test values) for which a causal relationship to the study drug was not ruled out were reported in 41.7% (40/96 subjects) in the placebo group, 54.8% (63/115 subjects) in the 600 mg group, and 61.3% (68/111 subjects) in the 1200 mg group. Common events included somnolence (2 subjects in the placebo group, 23 subjects in the 600 mg group, and 18 subjects in the 1200 mg group), dizziness (4 subjects in the placebo group, 11 subjects in the 600 mg group, and 26 subjects in the 1200 mg group), and headache (4 subjects in the placebo group, 11 subjects in the 600 mg group, and 12 subjects in the 1200 mg group).

AEs related to vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) were reported in 3 subjects in the placebo group (hypertension); 1 subject in the 600 mg group (hypertension); and 3 subjects in the 1200 mg group (hypotension, blood pressure increased, and hypertension, each in 1 subject).

As an ECG-related AE, bundle branch block was reported in 1 subject in the 1200 mg group.

In summary of the above, the study demonstrated the efficacy of gabapentin enacarbil 1200 mg given repeatedly for 12 weeks in non-Japanese patients with RLS, and raised no particular major concerns about the safety.

4) Overseas phase IV study [RXP114025]

This was a placebo-controlled, randomized, double-blind, parallel-group, comparative study to evaluate the efficacy and safety of gabapentin enacarbil in non-Japanese patients (target sample size 428 subjects; 107 subjects per group) with RLS diagnosed according to the diagnostic criteria established by the International RLS Study Group.

As for the dosage regimen, gabapentin enacarbil 300, 450, or 600 mg or placebo was administered orally once daily at 17:00 with a meal, with the duration of treatment set to 12 weeks.

Of the total of 501 subjects (125 subjects in the placebo group, 125 subjects in the 300 mg group, 125 subjects in the 450 mg group, and 126 subjects in the 600 mg group), the safety analysis set consisted of 487 subjects (121 subjects in the placebo group, 121 subjects in the 300 mg group, 123 subjects in the 450 mg group, and 122 subjects in the 600 mg group). The

efficacy analysis set consisted of 459 subjects (117 subjects in the placebo group, 111 subjects in the 300 mg group, 112 subjects in the 450 mg group, and 119 subjects in the 600 mg group).

The change from baseline in IRLS score at final evaluation in the MITT analysis set, which was a primary endpoint of the study, is shown in Table 6. The gabapentin enacarbil 450 mg and 600 mg groups showed statistically significant differences compared with the placebo group (P = 0.014 and P = 0.014, respectively; analysis of covariance adjusted for study site and baseline). The gabapentin enacarbil 300 mg group showed no statistically significant difference compared with the placebo group.

Table 6: Change from baseline in IRLS score at Week 12 using LOCF (MITT analysis set)

	Placebo n = 117	**GEn[1)] 300 mg n = 111**	**GEn 450 mg n = 112**	**GEn 600 mg n = 119**
Adjusted mean (SE)	−9.93 (0.753)	−11.48 (0.767)	−12.54 (0.764)	−12.50 (0.745)
Mean difference [2)]		−1.55	−2.61	−2.57
95% CI		(−3.63, 0.53)	(−4.68, −0.54)	(−4.62, −0.52)
P-value†		0.144	0.014	0.014

[1)] Gabapentin enacarbil

[2)] Calculated as "GEn group − Placebo group"

† Analysis of covariance adjusted for study site and baseline

AEs were reported in 55% (66/121 subjects) in the placebo group, 53% (64/121 subjects) in the 300 mg group, 59% (73/123 subjects) in the 450 mg group, and 56% (68/122 subjects) in the 600 mg group. SAEs were reported in 1 subject in the placebo group, 2 subjects in the 300 mg group, and 1 subject in the 600 mg group, but there were no deaths.

Common AEs included somnolence (8 subjects in the placebo group, 12 subjects in the 300 mg group, 20 subjects in the 450 mg group, and 13 subjects in the 600 mg group), headache (12 subjects in the placebo group, 10 subjects in the 300 mg group, 9 subjects in the 450 mg group, and 11 subjects in the 600 mg group), and dizziness (5 subjects in the placebo group, 5 subjects in the 300 mg group, 8 subjects in the 450 mg group, and 15 subjects in the 600 mg group). In summary of the above, the study demonstrated the efficacy, safety, and tolerability of gabapentin enacarbil 600 mg. The clinical effectiveness of gabapentin enacarbil 450 mg did not appear to exceed that of gabapentin enacarbil 600 mg.

5) Japanese post-marketing study in RLS patients with moderate renal impairment [CL-0103]

This was a multicenter, open-label, uncontrolled study (using a centralized registration method) in patients (target sample size, 50 subjects) who had moderate to severe idiopathic RLS diagnosed according to the diagnostic criteria established by the International RLS Study Group and who had moderate renal impairment, conducted to evaluate the safety, efficacy, and pharmacokinetics of gabapentin enacarbil and to determine the dosage regimen for

patients with renal impairment. The study consisted of a 1-week run-in period for observation, a 4-week treatment period for oral administration of gabapentin enacarbil tablets 300 mg once daily after the evening meal, and a 1-week follow-up period for post-treatment observation.

Although the planned sample size was not reached, the study was terminated at the planned end time of the study period, at which time informed consent had been obtained from 40 subjects. Of these 40 subjects who provided consent, 21 subjects were not enrolled for reasons such as not fulfilling the inclusion criteria or meeting any exclusion criteria, and the remaining 19 subjects were treated with gabapentin enacarbil. Of these 19 subjects treated with gabapentin enacarbil, 17 subjects completed the study, while 2 subjects were discontinued from the study. The reason for discontinuation was AE in 1 subject and subject's request in the other subject.

The change in IRLS score at each point of evaluation in the FAS, which was the primary endpoint of the study, is shown in Table 7. The mean (standard deviation) change in IRLS score at the end of treatment period was −9.1 (5.7), showing improvement in IRLS score. In terms of the secondary endpoints, the ICGI and PCGI responder rates increased over time, and at the responder rate at the end of treatment period, the ICGI responder rate was 68.4% and the PCGI responder rate was 78.9%.

In moderate to severe idiopathic RLS patients with moderate renal impairment, gabapentin enacarbil once daily 300 mg demonstrated symptomatic improvement of RLS.

Table 7: Change in IRLS score at each time point of evaluation: FAS

	Week 1	Week 2	Week 4	End of treatment period	Follow-up period
n	19	18	18	19	19
Mean	−4.4	−8.1	−9.4	−9.1	−7.4
standard deviation	5.8	5.9	5.6	5.7	7.1
Minimum	−14	−22	−22	−22	−24
Q1	−9.0	−11.0	−12.0	−12.0	−11.0
Median	−4.0	−6.5	−9.0	−9.0	−8.0
Q3	−2.0	−5.0	−7.0	−4.0	0.0
Maximum	8	0	-1	−1	3

The incidence of AEs in this study was 63.2% (12/19 subjects, 19 events). The incidence of AEs for which a causal relationship to the study drug was not ruled out was 36.8% (7/19 subjects, 11 events). There were no deaths or SAEs in this study. AEs leading to discontinuation of study treatment were reported in 2 subjects, of which a causal relationship to the study drug was not ruled out in 1 subject. The event severity was moderate for 1 event of rash in 1 subject, and all other 18 AEs were mild.

Relatively common AEs with an incidence of ≥ 10% were somnolence (15.8%, 3/19 subjects) and blood creatine phosphokinase increased (10.5%, 2/19 subjects). The only relatively common AE for which a causal relationship to the study drug was not ruled out was somnolence (15.8%, 3/19 subjects).

There were no deaths or SAEs. Laboratory test values showed no clinically relevant changes. In summary of the above, the safety and tolerability of gabapentin enacarbil 300 mg once daily in moderate to severe idiopathic RLS patients with moderate renal impairment raised no major concerns.

1.3 Summary of Key Safety Information for the Study Drug

Refer to the latest package insert for gabapentin enacarbil.

1.4 Risk Benefit Assessment

1.4.1 Risk Assessment

Gabapentin enacarbil is rapidly metabolized to gabapentin in the body following oral administration, and is excreted mostly as gabapentin renally into urine. Renally impaired patients may have delayed excretion of gabapentin. Severe renal impairment is a contraindication to gabapentin enacarbil. Administration of gabapentin enacarbil may cause increased body weight. Sleepiness, decreased attention, decreased mental concentration, decreased motor response, etc. may occur. Eye disorders such as blurred vision or accommodation disorder may occur.

In the Japanese phase II/III comparative study [CL-0003], adverse drug reactions, including abnormal laboratory test values, were reported in 68 (56.7%) of 120 subjects evaluated for safety. Common adverse drug reactions were dizziness (30 subjects, 25.0%), somnolence (23 subjects, 19.2%), and nausea (6 subjects, 5.0%).

In terms of the severity of AEs in Japanese clinical studies, the only severe AE was lymphoma in 1 subject who took 1200 mg in the Japanese long-term study [CL-0005]. For this AE of lymphoma, a causal relationship to the study drug was not ruled out, and the patient died of lymphoma. The incidence of moderate AEs in the placebo group, 600 mg group, 900 mg group, and 1200 mg group of the Japanese phase II/III comparative study [CL-0003] was 6.0% (7/116 subjects), 13.3% (16/120 subjects), 6.7% (8/119 subjects), and 14.0% (16/114 subjects), respectively, and that in the Japanese long-term study [CL-0005] was 28.0% (51/182 subjects). The incidence was slightly higher in the 600 mg and 1200 mg groups than in the placebo group in the Japanese phase II/III comparative study [CL-0003]. Moderate AEs reported in 2 or more subjects given gabapentin enacarbil were dizziness, somnolence, blood CPK increased, nausea, headache, AST increased, ALT increased, and back pain. Of these, dizziness and somnolence were reported in all gabapentin enacarbil groups. In addition, dizziness, somnolence, nausea, headache, and blood CPK increased were more common in the Japanese long-term study [CL-0005] than in the Japanese phase II/III comparative study [CL-0003].

A rat carcinogenicity study (2-year forced oral administration) showed carcinogenicity. At 5000 mg/kg/day (i.e., 90 times the human systemic exposure at 600 mg of gabapentin enacarbil as the clinical daily dose), occurrence of pancreatic acinar cell tumors (adenoma or adenocarcinoma) increased in both males and females, with a higher number of tumors in males than in females. At 2000 mg/kg/day (i.e., 40 times the human systemic exposure at 600 mg of gabapentin enacarbil as the clinical daily dose), males had increased pancreatic acinar cell tumors. At 500 mg/kg/day (i.e., 10 times the human systemic exposure at 600 mg of gabapentin enacarbil as the clinical daily dose), no effects were observed. In mice, no carcinogenicity was observed in males or females. In clinical studies conducted to date inside and outside Japan, and in periodic safety reports, no cases of pancreatic tumors have been reported.

With gabapentin, the active metabolite of gabapentin enacarbil, acute renal failure, oculomucocutaneous syndrome (Stevens-Johnson syndrome), drug-induced hypersensitivity syndrome, hepatitis, hepatic function disorder, jaundice, rhabdomyolysis, and anaphylaxis have been reported as clinically significant adverse reactions. Thus, these events can occur in this study as well. Unexpected AEs may also occur.

In a review of 199 placebo-controlled overseas clinical studies of multiple antiepileptic drugs that included gabapentin as the active metabolite of gabapentin enacarbil in patients with epilepsy, psychiatric diseases, etc., the risk of suicidal ideation and suicide attempt in the antiepileptic medication group was approximately 2-fold higher than that in the placebo group (0.43% in the antiepileptic medication group and 0.24% in the placebo group), with the incidence higher by 1.9 per 1000 persons (95% confidence interval, 0.6-3.9) in the antiepileptic medication group compared with the placebo group, or by 2.4 per 1000 persons in a subgroup of patients with epilepsy.

1.4.2 Benefit Assessment

Oral administration of gabapentin enacarbil can improve moderate to severe idiopathic RLS symptoms and impaired QOL associated with RLS.

2 STUDY OBJECTIVES, DESIGN, AND ENDPOINTS

2.1 Study Objectives

- To verify the efficacy of oral gabapentin enacarbil 600 mg once daily compared with placebo on the basis of the change from baseline in IRLS score in patients with moderate to severe idiopathic restless legs syndrome (RLS), using a multicenter, randomized, double-blind, parallel-group, comparative design

- To evaluate the safety of gabapentin enacarbil 600 mg

2.2 Study Design and Dose Rationale

2.2.1 Study Design

Gabapentin enacarbil 600 mg or placebo will be administered orally once daily after the evening meal. Patients meeting the inclusion and exclusion criteria at provisional registration will receive single-blind placebo for 1 week (run-in period). Of these, patients meeting the inclusion and exclusion criteria at formal registration will be randomized to receive double-blind treatment with either gabapentin enacarbil 600 mg or placebo for 12 weeks (treatment period). After the end of the 12-week treatment period, single-blind placebo will be given for 1 week (follow-up period) for follow-up observation.

However, of the patients meeting the inclusion and exclusion criteria at formal registration, those with an estimated creatinine clearance of ≥ 60 to < 90 mL/min at the start of the run-in period will receive randomized double-blind treatment initially with either gabapentin enacarbil 300 mg or placebo for 1 week (upward titration period) followed by gabapentin enacarbil 600 mg or placebo for 11 weeks, totaling 12 weeks (treatment period including the upward titration period).

Stratified allocation will be performed with stratification factors of age (< 50 years and ≥ 50 years) at the start of the run-in period and estimated creatinine clearance (≥ 60 to < 90 mL/min and ≥ 90 mL/min) at the start of the run-in period.

2.2.2 Dose Rationale

[Rationale for the dosage]

The dosage and administration stated in the Japanese package insert for Regnite Tablets is "The usual adult dose for oral use is 600 mg (as gabapentin enacarbil) once daily after dinner." However, the efficacy of gabapentin enacarbil 600 mg was not verified by the primary analysis of the Japanese phase II/III study [CL-0003]. Thus, this study has been planned to verify the efficacy of gabapentin enacarbil 600 mg/day and also to evaluate the safety.

The mode and duration of administration have been set to once daily for 12 weeks, as in the Japanese phase II/III study [CL-0003]. Gabapentin enacarbil is considered to require dose adjustment according to renal function, because it is a renally excreted drug, and Japanese and overseas studies in patients with renal impairment showed prolonged elimination half-life and increased Cmax and AUCinf of gabapentin (active metabolite of gabapentin enacarbil) in plasma in association with impaired renal function. Thus, for patients with an estimated creatinine clearance of ≥ 60 to < 90 mL/min at the start of the run-in period, a 1-week upward titration period for administration at the starting dose of 300 mg has been employed with reference to the package insert, aiming to verify the efficacy of 600 mg/day while securing the safety of the subjects. A 1-week run-in period has been set to confirm the eligibility against the inclusion and exclusion criteria at formal registration. A 1-week follow-up period has been set to check for withdrawal symptoms after the end of administration of the study drug in the treatment period.

2.3 Endpoints

2.3.1 Primary Endpoint

- Change from baseline in IRLS score at the end of treatment period (Week 12)

[Rationale for the primary endpoint]

The IRLS is used because it is generally used for evaluation of drug efficacy for RLS.

2.3.2 Secondary Endpoints

- Change from baseline in IRLS score at each time point
- ICGI responder rate
- PCGI responder rate
- Change from baseline in Pittsburgh Sleep Quality Index [Yuriko et al., 2000; Doi et al., 1998; Buysse et al., 1989]
- Change from baseline in Athens Insomnia Scale [Soldatos et al., 2000]
- Change from baseline in RLS Pain score [Jensen et al., 1986]
- Change from baseline in EQ-5D-5L [Herdman et al., 2011]

[Rationale for the secondary endpoints]

These endpoints have been set with reference to the Japanese phase II/III study [CL-0003], for evaluation for the marketing approval.

The ICGI and PCGI have been employed to evaluate the clinical significance of the treatment, because these are the standardized tools widely used in neuropharmacological studies and are the parameters of overall evaluation.

The Pittsburgh Sleep Quality Index has been employed because it is a sleep parameter widely used in Japan.

The Athens Insomnia Scale has been employed to evaluate sleep because it is an evaluation tool based on the global insomnia assessment criteria issued by the Worldwide Project on Sleep and Health, established World Health Organization (WHO) and other organizations.

The RLS Pain score has been employed to evaluate pain.

The EQ-5D-5L has been employed because it is a QOL assessment tool used widely also for health economic evaluation, etc.

2.3.3 Safety Endpoints

- Vital signs
- Adverse events
- Laboratory tests
- Body weight
- Epworth Sleepiness Scale [Murray, 1991]

3 STUDY POPULATION

3.1 Selection of Study Population

Patients with moderate to severe idiopathic restless legs syndrome (RLS)

Patients with RLS diagnosed according to the 2014 updated diagnostic criteria for RLS by the International RLS Study Group [Allen et al., 2014]; RLS will be diagnosed when all of the following 5 diagnostic criteria are met:

1. An urge to move the legs usually accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, or habitual foot tapping).

In addition, the following four features support the diagnosis:

1. Presence of periodic leg movements in sleep or at rest
2. Reduction in discomfort with dopamine receptor agonist treatment
3. Family history of RLS among first-degree relatives
4. Lack of profound daytime sleepiness

[Rationale for the target disease]

To verify the efficacy and safety of gabapentin enacarbil compared with placebo in patients with RLS

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

At provisional registration:

1. Provided written informed consent using the informed consent form approved by the Institutional Review Board (IRB) prior to any study-related procedures (including discontinuation of excluded concomitant medications)
2. Male or female outpatient aged between ≥ 20 and ≤ 80 years at the time of consent

3. Patient with a diagnosis of RLS according to the International RLS Study Group diagnostic criteria for RLS (2014 update)
4. Had RLS symptoms for ≥ 15 days during the month prior to the start of the run-in period, or if on treatment for RLS, during the month prior to the start of that treatment
5. Has an International Restless Legs Syndrome Rating Scale (IRLS) score of ≥ 15 at the start of the run-in period
6. Has not taken dopamine agonists, dopamine preparations, gabapentin, gabapentin enacarbil, or pregabalin during at least one week before the first day of the run-in period
7. Has not received other treatments for RLS (opioids, benzodiazepines, long-acting dopamine agonists) during at least 2 weeks before the first day of the run-in period
8. Female subject must either:

   Be of nonchildbearing potential:

   - Postmenopausal (defined as no menstruation for at least 1 year) at the start of the run-in period, or
   - Documented surgically sterile

   Or, if of childbearing potential,

   - Agree not to become pregnant during the study and for 28 days after the final study drug administration,
   - And have a negative pregnancy test at the start of the run-in period
   - And if heterosexually active, agree to consistently use two (one or both of which must be the barrier method) of the established forms of birth control* specified below, during the study period and for 28 days after the final study drug administration

   *Established forms of birth control include:

   - Correct usage of approved oral contraceptives
   - Intrauterine device (IUD), intrauterine system (IUS), and other intrauterine instruments
   - Barrier method with male condoms or female condoms
   - Rhythm method (Knaus-Ogino method)
9. Female subject must agree not to breastfeed throughout the study period and for 28 days after the final study drug administration.
10. Female subject must not donate ova throughout the study period and for 28 days after the final study drug administration.
11. Agrees not to participate in another interventional study during the study period.
12. Has a body mass index (BMI) range of 18.5 to < 30 (BMI = Body weight (kg)/Height $(m)^2$).

At formal registration:

13. Has an IRLS score of ≥ 15 at the start of the treatment period

14. Has RLS symptoms (evenings and nights) for at least 4 days during the 1-week run-in period
15. Has an estimated creatinine clearance value* of ≥ 60 mL/min as calculated using the Cockcroft-Gault equation at the start of the run-in period.

    *For calculation of the estimated creatinine clearance, refer to ***Section 5.7 Other Measurements, Assessments or Methods.***

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

At provisional registration:

1. A sleep disorder (e.g., sleep apnea) that may affect the assessment of RLS
2. A history of RLS symptom augmentation or post-therapy rebound with previous dopamine agonist treatment
3. Neurologic disease or movement disorder (e.g., neurologic disease, Parkinson's disease, multiple sclerosis, dyskinesia, dystonia, rheumatoid arthritis)
4. Poorly controlled diabetes mellitus (i.e., HbA1c > 7.5% [NGSP-value] on a test during the past 6 months), iron deficiency anemia, or current use of oral sedative-hypnotics
5. Has a history of suicide attempt within 6 months before consent, or judged by the investigator/sub-investigator to be at risk for suicide
6. Has elevated ALT or AST (based on laboratory data within the past 6 months) (For reference, grade ≥ 2 according to the "Criteria for Seriousness/Severity Grading of Adverse Drug Reactions," [Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, dated June 29, 1992] will be used.)
7. Moderate or severe depression (DSM-V)
8. Previously had alcohol dependence or drug poisoning, or within the past year had substance abuse or dependence
9. Shift worker (including night-work), professional driver, or dangerous machinery operator
10. Clinically significant or unstable medical conditions (e.g., current or past history of cancer, complication of serious cardiac disease*, hepatic disease*, renal disease*, hematological disease*, immunodeficiency, psychiatric disease).
    *For reference, Grade 3 of the "Criteria for Seriousness/Severity Grading of Adverse Drug Reactions," (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, dated June 29, 1992) will be used.
11. History of hypersensitivity to gabapentin
12. Had previously taken pregabalin, gabapentin enacarbil, or ASP8825 (including GSK1838262 and XP13512) as an investigational drug

13. Participated within 12 weeks (84 days) before the first day of the run-in period, or currently participating, in a clinical trial or post-marketing clinical study of another drug or a medical device.
14. Is employed by the Sponsor or the CRO, SMO, or study site involved in this study
15. Other subjects for whom participation in this study is judged to be inappropriate in the opinion of the investigator/sub-investigator

At formal registration:

16. Has a decrease in IRLS score at the start of the treatment period by 10 or more points from the start of the run-in period
17. Has clinically relevant abnormalities on laboratory tests* in the opinion of the investigator/sub-investigator
    *For reference, Grade 3 of the "Criteria for Seriousness/Severity Grading of Adverse Drug Reactions," (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, dated June 29, 1992) will be used.
18. Poorly controlled diabetes mellitus (i.e., HbA1c > 7.5% [NGSP-value] on a laboratory test in the run-in period)
19. Serum ferritin < 12 ng/mL on a laboratory test at the start of the run-in period
20. Elevated ALT or AST on laboratory tests at the start of the run-in period (For reference, grade ≥ 2 according to the "Criteria for Seriousness/Severity Grading of Adverse Drug Reactions," [Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, dated June 29, 1992] will be used.)
21. Female other than female of nonchildbearing potential judged to be pregnant based on the pregnancy test in the run-in period (in line with the inclusion criterion 8)
22. Subjects for whom participation in this study is judged to be inappropriate in the opinion of the investigator/sub-investigator

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENT

4.1 Identification of Study Drug

4.1.1 Test Drug

The test drug (gabapentin enacarbil tablets 300 mg) to be given as a study drug during the treatment period is described below:

Substance code	ASP8825
Generic name	Gabapentin enacarbil
Chemical name	(1-{[({(1*RS*)-1-[(2-Methylpropanoyl)oxy]ethoxy}carbonyl)amino]methyl}cyclohexyl)acetic acid
Molecular formula and molecular weight	$C_{16}H_{27}NO_6$ (Molecular weight: 329.39)
Strength and dosage form	Plain white tablets, each containing 300 mg of gabapentin enacarbil
Manufacturer	Astellas Pharma Inc.
Lot number	See the Procedures for Handling Study Drugs.
Storage conditions	Store at room temperature.

4.1.2 Comparative Drug

The comparative drug (placebo matching gabapentin enacarbil tablets) to be given as a study drug during the treatment period is described below:

Strength and dosage form	Plain white tablets not containing gabapentin enacarbil, indistinguishable in appearance from the gabapentin enacarbil tablets 300 mg
Manufacturer	Astellas Pharma Inc.
Lot number	See the Procedures for Handling Study Drugs.
Storage conditions	Store at room temperature.

4.1.3 Study drug for the run-in period and study drug for the follow-up period

The study drug to be given during the run-in period and the follow-up period is described below. The study drug for the run-in period and the follow-up period is the same as the comparative drug to be given during the treatment period in terms of the strength and dosage form.

Strength and dosage form	Placebo matching gabapentin enacarbil tablets: Plain white tablets not containing gabapentin enacarbil, indistinguishable in appearance from the gabapentin enacarbil tablets 300 mg
Manufacturer	Astellas Pharma Inc.
Lot number	See the Procedures for Handling Study Drugs.
Storage conditions	Store at room temperature.

4.2 Packaging and Labeling

All study drugs used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at Astellas Pharma Inc., in accordance with the standard operating procedures (SOPs) of Astellas Pharma Inc., Good Manufacturing Practice (GMP) guidelines, GCP, and applicable local laws and regulations.

1. Packaging

The study drugs for the run-in period and the follow-up period will be packaged in bottles for each dose. Each bottle will contain 2 tablets of the placebo matching gabapentin enacarbil tablets, together with a desiccant. Ten bottles of the study drug for the run-in period or the follow-up period will be packaged in one box.

The study drugs for the treatment period (including the upward titration period) will be packaged in bottles for each dose. Each bottle will contain a total of 2 tablets of either or both of the test drug (gabapentin enacarbil tablets 300 mg) and/or the comparative drug (placebo matching gabapentin enacarbil tablets), together with a desiccant. Ten bottles of the study drug will be packaged in one box for prescription at Week 0 and Week 1 of the treatment period, and 17 bottles will be packaged in one box for prescription at the other scheduled visits.

The combination of the test drug and the comparative drug in each group is shown below:

Treatment group	Run-in period (1 week)	Treatment period (12 weeks)		Follow-up period (1 week)
		Upward titration period (1 week)	(11 weeks)	
Placebo group	○○	○○	○○	○○
600 mg group (Patients with an estimated creatinine clearance of ≥ 90 mL/min at the start of the run-in period)	○○	●●	●●	○○
600 mg group (Patients with an estimated creatinine clearance of ≥ 60 to < 90 mL/min at the start of the run-in period)	○○	○●	●●	○○

●: Gabapentin enacarbil tablets 300 mg. ○: Placebo matching gabapentin enacarbil tablets.

2. Box labeling

Each box of the study drugs for the run-in period, treatment period, or follow-up period will be labeled as below.

Study drug for the run-in period and the follow-up period and the treatment period (for prescription at Week 0 and Week 1) (Sample):

Top surface

For use in post-marketing clinical study only

Lot No.8825-CL-0101
20 tablets (2 tablets × 10 bottles)

Gabapentin enacarbil post-marketing clinical study

Note:

1. This box contains the study drug to be taken once daily after the evening meal for 10 days.
2. The study drug should be opened immediately before administration, and both of the two tablets in one bottle should be taken at a time.
3. Be careful not to take the desiccant, contained in the bottle along with the study drug.
4. Do not take any remaining portions of the study drug, but please make sure to bring them along with the bottles and box at the next visit.

Storage conditions: Store at room temperature.
Expiration date: Specified in the Procedures for Handling the Study Drugs.

Astellas Pharma Inc.
2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo

Front surface

For use in post-marketing clinical study only

Lot No. 8825-CL-0101

Gabapentin enacarbil post-marketing clinical study

Study drug for the treatment period (for prescription at Weeks 2–10) (Sample):

Top surface

For use in post-marketing clinical study only

Lot No.8825-CL-0101
34 tablets (2 tablets × 17 bottles)

Gabapentin enacarbil post-marketing clinical study

Note:

1. This box contains the study drug to be taken once daily after the evening meal for 17 days.
2. The study drug should be opened immediately before administration, and both of the two tablets in one bottle should be taken at a time.
3. Be careful not to take the desiccant, contained in the bottle along with the study drug.
4. Do not take any remaining portions of the study drug, but please make sure to bring them along with the bottles and box at the next visit.

Storage conditions: Store at room temperature.
Expiration date: Specified in the Procedures for Handling the Study Drugs.

Astellas Pharma Inc.
2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo

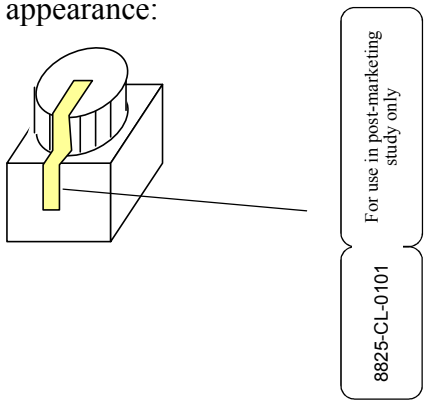
Front surface

For use in post-marketing clinical study only

Lot No. 8825-CL-0101

Gabapentin enacarbil post-marketing clinical study

Bottle appearance:



4.3 Study Drug Handling

The head of the study site or the study drug storage manager should take accountability of the study drugs as following issues:

- The study drug storage manager should store and take accountability of the study drugs in accordance with the procedures for handling the study drugs written by the Sponsor.
- The study drug storage manager should prepare and retain records of the study drug's receipt, the inventory at the study site, the use by each subject, and the return to the Sponsor or alternative disposal of unused study drugs. These records should include dates, quantities, lot numbers, expiration dates (if applicable), and the subject numbers.
- The study drug storage manager should prepare and retain records that document adequately that the subjects were provided the doses specified by the protocol, and reconcile all the study drugs supplied from the Sponsor.

4.4 Blinding

4.4.1 Blinding Method

This study will compare the gabapentin enacarbil 600 mg group and the placebo group in terms of the efficacy and safety in a double-blind manner (except for the run-in period and the follow-up period, performed in a single-blind manner). The gabapentin enacarbil tablet 300 mg and the placebo matching gabapentin enacarbil tablet will be indistinguishable from one another in appearance, and packaging for each treatment group will also be indistinguishable in appearance.

Access to the treatment codes will be available only to the person responsible for study drug randomization (including his/her assistant) and designated personnel authorized to open the code for Suspected Unexpected Serious Adverse Reaction (SUSAR) case reporting.

4.4.2 Confirmation of the Indistinguishability of the Study Drugs

The indistinguishability in appearance of the study drugs and their packages will be checked by the trustees for manufacturing and packaging or storing the study drugs at the following time points, and will be determined by the Quality Assurance Quality Technology department:

- Before delivery to the study site: Checked by the trustee for manufacturing and packaging the study drugs
- Between completion of the study drug administration and treatment code breaking: Checked by the trustee for storing the study drugs

4.4.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

1) Retention of the Treatment Codes

The person responsible for study drug randomization will prepare and separately seal one original and one copy of each treatment code. The person responsible for study drug randomization will retain the original, while the Sponsor will retain the copy, of the treatment

code until the time of the treatment code breaking. In addition, the person responsible for study drug randomization will prepare the treatment codes for emergency and seal them after randomization. The sealed treatment codes for emergency will be retained by the person responsible for treatment codes for emergency. The treatment codes for emergency will be able to be opened individually, and will be controlled by the person responsible for treatment codes for emergency via a Web-based system.

2) Treatment Code Breaking

After completion of administration of the study drugs and after the eCRF data are locked and handling of the data is decided, the person responsible for study drug randomization will open the original assignment schedule. The person responsible for study drug randomization will then submit the original assignment schedule to the Sponsor and document the submission record.

4.4.4 Breaking the Treatment Code for Emergency

In any medical emergency where the study drug needs to be identified to be either gabapentin enacarbil tablets 300 mg or placebo, the investigator/sub-investigator may request the sponsor's responsible person to break the treatment code for emergency for a given subject. The sponsor's responsible person will judge appropriateness of breaking the treatment code for emergency and, if appropriate, open the code in accordance with the "Procedures for emergency code breaking for gabapentin enacarbil post-marketing clinical study." The investigator/sub-investigator, sponsor's responsible person, and the person responsible for treatment codes for emergency will communicate with each other to allow for prompt breaking of the treatment code for emergency. The sub-investigator may request for breaking the treatment code for emergency, in principle after prior agreement of the investigator. However, if prior agreement of the investigator cannot be obtained, the sub-investigator will promptly notify the investigator of the request.

4.4.5 Breaking the Treatment Code by the Sponsor

The Sponsor may break the treatment code for subjects who experience an SUSAR, in order to determine whether the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will be provided to the limited staff who are responsible to break the codes for all SUSAR cases for reporting purposes.

The treatment code for each randomized subject will be provided by the person managing treatment codes for emergency or the Interactive Response Technology (IRT) in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The time, date, subject number, and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file. They must only be requested by the investigator or other persons designated as sub-investigators. The need for expedited regulatory reporting of the SUSAR will be judged only by the designated personnel of the safety management

department. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure.

Unblinding of the study medication should only be considered for subject safety or when clinical therapeutic decisions are contingent upon knowing the blinded study drug assignment. Any unblinding by the study staff must be reported immediately to the Sponsor and must include an explanation of why the study medication was unblinded. If possible, the Sponsor should be contacted prior to unblinding of the study medication.

4.5 Assignment and Allocation

The person responsible for study drug randomization will prepare the treatment codes for randomization of the study drug for the double-blind period, and retain them under lock and key until the time of treatment code breaking.

Stratified allocation will be performed with stratification factors of age (< 50 years and ≥ 50 years) at the start of the run-in period and estimated creatinine clearance (≥ 60 to < 90 mL/min and ≥ 90 mL/min) at the start of the run-in period, to minimize imbalance in subject characteristics between the treatment groups to allow for proper comparison. The patient registration center will assign the drug numbers to the subjects in accordance with the patient registration procedures.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug and Other Medications

5.1.1 Dose, Dosage Regimen, and Administration Period

[Dose]

- Gabapentin enacarbil 600 mg group: 600 mg/day of gabapentin enacarbil
- Placebo group: 0 mg/day of gabapentin enacarbil

[Dosage regimen and administration period]

Two tablets will be administered orally once daily after the evening meal.

Treatment group	Run-in period (1 week)	Treatment period (12 weeks)		Follow-up period (1 week)
		Upward titration period (1 week)	(11 weeks)	
Placebo group (0 mg/day)	○○	○○	○○	○○
600 mg group (600 mg/day) (Patients with an estimated creatinine clearance of ≥ 90 mL/min at the start of the run-in period)		●●	●●	
600 mg group (600 mg/day) (Patients with an estimated creatinine clearance of ≥ 60 to < 90 mL/min at the start of the run-in period)		○●	●●	

●: Gabapentin enacarbil tablets 300 mg. ○: Placebo matching gabapentin enacarbil tablets

5.1.2 Increase or Reduction in Dose of the Study Drug

No dose reduction will be performed in this study. For patients in the gabapentin enacarbil group with an estimated creatinine clearance of ≥ 60 to < 90 mL/min at the start of the run-in period, the starting dose will be 300 mg given for 1 week, and the dose will be increased to 600 mg with careful monitoring of the subject's condition for possible occurrence of AEs.

5.1.3 Previous and Concomitant Treatment (Medication and Non-medication Therapy)

5.1.3.1 Previous Treatment (Medications and Non-medication Therapies)

Use of the following drugs before the start of the run-in period will require the specified washout period:

1) Dopamine agonists, dopamine preparations, gabapentin: ≥ 7 days
2) Opioids, benzodiazepines (for only if used to treat RLS), long-acting dopamine agonists: ≥ 14 days

Previous medication and previous non-medication therapy are defined respectively as the medication and non-medication therapy used by the day before the start of the run-in period. In terms of all previous medications and therapies up to 28 days before the start of the run-in period, the data below will be collected and recorded on the eCRF. No recording on the eCRF will be required for drugs used to treat common cold or other transient conditions or past otorhinolaryngologic diseases, dental diseases, skin diseases, ophthalmologic diseases, etc., or for pre-treatment before endoscopy, etc.

- Previous medication: name of the drug, route of administration, duration of treatment, therapy dates, reason for use
- Previous non-medication therapy: name of the therapy, duration of treatment, therapy dates, reason for use

5.1.3.2 Concomitant Treatment (Medication and Non-medication Therapy)

For all drugs and therapies used after the start of the run-in period through the end of the study period, the following data will be recorded on the eCRF:

- Concomitant medication: name of the drug, route of administration, therapy duration, therapy dates, reason for use
- Concomitant non-medication therapies: name of the therapy, therapy duration, therapy dates, reason for use

[Excluded concomitant medications/therapies, etc.]

1) Concomitant use of the following drugs will be prohibited from 14 days before the first day of the run-in period through the end of the study period:
- Benzodiazepines (for only if used to treat RLS): clonazepam, etc.
- Opioids: codeine, oxycodone, morphine, etc.
- Long-acting dopamine agonists: cabergoline, etc.

2) Concomitant use of the following drugs will be prohibited from 7 days before the first day of the run-in period through the end of the study period:
- Dopamine agonists: pramipexole (BI-Sifrol), talipexole, rotigotine (Neupro Patch), ropinirole, etc.
- Dopamine preparations: levodopa/carbidopa combined drug, etc.
- Gabapentin: Gabapen
- Gabapentin enacarbil: Regnite
- Pregabalin: Lyrica

3) Concomitant use of the following drugs will be prohibited from the first day of the run-in period through the end of the study period:
- Dopamine receptor inhibitors: Primperan (metoclopramide), Nauzelin (domperidone), etc.
- Central depressants (hypnotics, antianxiety drugs, antipsychotic drugs, antidepressants, antimanic drugs, antiepileptic drugs)
- Magnesium preparations[*1], iron preparations[*1], folic acid[*1], vitamin B12 preparations[*1]
- Other investigational products or post-marketing clinical study drugs

[*1]These apply to prescription drugs

4) The following drugs are prohibited for concomitant use from 7 days before a visit (day of IRLS score assessment) until the time of the IRLS score assessment at the visit, between the first day of the run-in period and the end of the study period:
   - Antihistamines

[Rationale for the excluded concomitant medications/therapies, etc.]

These drugs/therapies are prohibited to avoid possible effects on evaluation of the efficacy of gabapentin enacarbil.

5.1.4 Treatment Compliance

The treatment compliance status of each subject will be recorded on the eCRF at each visit.

At dispensing of the study drug to the subject, the investigator/sub-investigator and the study drug storage manager will explain how to take the study drug, with particular caution to the following:

1) The subject must never take more one dose at a time, even if a dose of the study drug has been missed.
2) The subject must bring the remaining study drug and empty bottles at the next visit.

The investigator/sub-investigator or clinical research coordinator will record each subject's treatment compliance status during the study period on the eCRF, based on the study drug prescription date, number of the study drugs prescribed, number of the study drugs retrieved, number of the study drugs lost, start and end date of administration, interview with the subject, etc. If the compliance rate is judged to be problematic, the reason will be investigated, and instruction on proper medication will again be given to the subject to improve the compliance rate.

5.1.5 Emergency Procedures and Management of Overdose

If gabapentin enacarbil overdose has caused certain symptoms, the investigator/sub-investigator will perform emergency treatment according to the symptoms, and secure the safety of the subject. Oral administration of gabapentin enacarbil up to 6 g has been reported overseas. Typical symptoms of overdose have been psychomotor retardation, vertigo, sedation, and somnolence. In the event of overdose, symptomatic treatment should be given. Gabapentin, which is the active metabolite of gabapentin enacarbil, can be removed by hemodialysis. Implementation of hemodialysis should be considered depending on the symptoms.

5.1.6 Criteria for Continuation of Treatment

Study treatment will not be extended in this study.

5.1.7 Restrictions During the Study

The investigator/sub-investigator will explain the compliance rules to the subjects, with particular caution to the following, when explaining how to take the study drug, etc.:

- Subjects will visit the study site according to the schedule stipulated in the protocol, and undergo scheduled tests and other procedures.
- Subjects are not allowed to take drugs that may affect assessment of the drug efficacy on the target disease (excluded concomitant medications) during the study period. The use of magnesium preparations, iron preparations, over-the-counter drugs or supplements containing folic acid or vitamin B12, and dietary supplements should be avoided as far as possible. Subjects are not allowed to take other drugs (including over-the-counter drugs such as combination cold remedies) at their own discretion without approval by the investigator, etc. If subjects desire to use such drugs, they should consult the investigator, etc. first.
- Subjects should notify the investigator/sub-investigator as far as possible beforehand if they will visit another hospital/department, newly visit another hospital/department, or use other drugs, including over-the-counter drugs, than those prescribed by the investigator/sub-investigator. If not beforehand, the investigator/sub-investigator should be notified afterwards.
- Subjects should use contraceptives during the study period, in line with inclusion criteria 8 to 10.
- Subjects with a history of regular alcohol consumption should avoid drinking alcohol during the study period as instructed by the investigator/sub-investigator.
- Subjects should store the study drug at room temperature.
- Subjects should take the study drug once daily after the evening meal, with water and without chewing or crushing the tablet. If a dose is missed after the evening meal, the dose may only be taken before bedtime.
- Subjects should take each dose of the study drug as instructed by the investigator/sub-investigator. When a dose is missed, the missed dose should not be taken together with the next dose.
- The study drug should not be taken with alcohol.
- Subjects should return any remaining portions of the study drug due to missed doses, etc., to the investigator/sub-investigator, and report the compliance status.
- If a subject has stopped taking the study drug at his or her own discretion, the subject should visit the study site as early as possible to undergo physical assessment by the investigator/sub-investigator.

Since the study drug may cause dizziness or sleepiness, subjects should be advised to exercise caution when working in high places, driving, or operating potentially hazardous machinery, etc.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

The investigator/sub-investigator will collect the data below at the time of informed consent (or at provisional registration) via a medical interview, etc., and check the eligibility (see ***Section 3.2 Inclusion Criteria*** and ***Section 3.3 Exclusion Criteria***). At the time of formal registration, the investigator/sub-investigator will again check the eligibility (see ***Section 3.2 Inclusion Criteria*** and ***Section 3.3 Exclusion Criteria***) and enter the details on the eCRF.

1) Sex, date of birth
2) Height, body weight
3) Family history (RLS)
4) Date of informed consent

5.2.2 Medical History

At selection of potential subjects, the investigator/sub-investigator will collect information on past diseases and concurrent diseases on the basis of existing medical records. Also at the time of informed consent as necessary, information on past diseases and concurrent diseases will be collected by way of medical interview with each potential subject. Patients should be excluded from this study if the collected information meets any of the exclusion criteria.

1) Past diseases

(1) Diseases that already resolved at the start of the run-in period are regarded as past diseases.

2) Concurrent diseases

(1) Diseases that have not resolved at the start of the run-in period are regarded as concurrent diseases.

(2) For the concurrent diseases judged by the investigator/sub-investigator to be present at the start of the run-in period, the diagnoses will be entered on the eCRF.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

The investigator/sub-investigator will collect information on the diagnosis, time of onset, and current symptoms (according to the RLS diagnostic criteria established by the International RLS Study Group) by way of medical interview, etc. at the time of informed consent (or at provisional registration), and enter the following data on the eCRF:

- Time of onset of the target disease (RLS)

5.3 Efficacy Assessment

The following data will be collected and entered on the eCRF:

Both the investigator/sub-investigator and the subjects will assess symptoms without referring to previous assessments. The investigator/sub-investigator should not answer questions from the subjects regarding previous assessments.

[Primary endpoint]

IRLS score: Week −1 (run-in period), Week 0 (baseline), Week 1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 13 (follow-up period), discontinuation

[Secondary endpoints]

1) ICGI and PCGI: Week 1, Week 2, Week 4, Week 8, Week 12, Week 13 (follow-up period), discontinuation
2) Pittsburgh Sleep Quality Index: Week 0 (baseline), Week 4, Week 8, Week 12, discontinuation
3) Athens Insomnia Scale: Week 0 (baseline), Week 4, Week 8, Week 12, discontinuation
4) RLS Pain score: Week −1 (run-in period), Week 0 (baseline), Week 1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 13 (follow-up period), discontinuation
5) EQ-5D-5L: Week 0 (baseline), Week 4, Week 8, Week 12, discontinuation

5.4 Safety Assessment

The following data will be collected and entered on the eCRF:

5.4.1 Vital Signs

Vital signs (sitting blood pressure and sitting pulse rate): Week −1 (run-in period), Week 0 (baseline), Week 1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, discontinuation

5.4.2 Adverse Events

Abnormal findings noted after the start of the run-in period will be collected. See ***Section 5.5 Adverse Events and Other Safety Aspects***, for information regarding AE collection and data handling.

5.4.3 Laboratory Assessments

Specimens for the hematology tests, biochemistry tests, thyroid function tests, and urinalysis (qualitative) below will be collected at the study site. The laboratory will retrieve the specimens and perform measurements.

The laboratory will report the measurement results to the investigator/sub-investigator and the Sponsor using the test result report form. The investigator/sub-investigator will confirm the data on the test result report form, enter the date of confirmation, comments, and signature or seal, and appropriately retain the test result report form. For any laboratory data outside the normal range, the investigator/sub-investigator will assess the clinical significance, and record the result in the source document.

The following data will be entered on the eCRF:

1. Hematology tests: Week −1 (run-in period), Week 0 (baseline), Week 2, Week 4, Week 8, Week 12, discontinuation

Red blood cell count, white blood cell count, white blood cell differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), platelet count, hemoglobin, hematocrit, MCV

2. Biochemistry tests: Week −1 (run-in period), Week 0 (baseline), Week 2, Week 4, Week 8, Week 12, discontinuation

Serum total protein, serum albumin, total bilirubin, ALP, ALT, AST, γ-GTP, calcium, chloride, potassium, sodium, inorganic phosphorus, glucose, serum creatinine, urea nitrogen, uric acid, CPK, HbA1c*

*Week −1 (run-in period) only

3. Thyroid function tests: Week 0 (baseline), Week 12, discontinuation

TSH, free T_4

4. Urinalysis (qualitative): Week −1 (run-in period), Week 0 (baseline), Week 2, Week 4, Week 8, Week 12, discontinuation

Protein, glucose, urobilinogen

5. Immunology test: Week −1 (run-in period)

Ferritin

5.4.4 Physical Examination

Body weight: Week −1 (run-in period), Week 0 (baseline), Week 4, Week 8, Week 12, discontinuation

5.4.5 Imaging

Not applicable.

5.4.6 Other

Epworth Sleepiness Scale: Week 0 (baseline), Week 1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 13, discontinuation

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An AE is any untoward medical occurrence in a subject, temporally associated with the use of the study drug, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the study drug.

For AEs noted during the run-in period, the event term, event onset date, time to event onset, event end date, severity, seriousness, other actions taken, and outcome will be entered on the eCRF.

For AEs noted during the treatment period, the event term, event onset date, time to event onset, event end date, severity, seriousness, action taken with the study drug, other actions taken, outcome, causal relationship to the study drug for the treatment period, and basis for the causality assessment will be collected and entered on the eCRF. However, the basis for the causality assessment will be required on the eCRF only for SAEs, AEs leading to discontinuation, and other AEs for which description of the basis is requested by the sponsor. In addition, as necessary, the investigator will record details of the treatment and clinical course in an appropriate document.

AEs during the follow-up period will also be collected, and the event term, event onset date, time to event onset, event end date, severity, seriousness, action taken with the study drug, causal relationship to the study drug for the treatment period, basis for the causality assessment, other actions taken, and outcome will be entered on the eCRF. However, the basis for the causality assessment will be required on the eCRF only for SAEs, AEs leading to discontinuation, and other AEs for which description of the basis is requested by the sponsor. In addition, as necessary, the investigator will record details of the treatment and clinical course in an appropriate document.

Whenever a diagnosis is determined on the basis of signs or symptoms, the diagnosis should be recorded rather than individual signs and symptoms. When no diagnosis can be determined on the basis of signs or symptoms, the investigator/sub-investigator will handle individual signs and symptoms as AEs. If an AE once disappeared but recurred, then the recurrence will be recorded as a new AE. If an AE is judged to have worsened in severity, then the worsening will be handled as a new AE. In addition, worsening of a concurrent disease will be handled as an AE.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, physical examination) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study drug
- The abnormality or test value is clinically significant in the opinion of the investigator.

5.5.2 Definition of Serious Adverse Events (SAEs)

An AE is considered “serious” if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life-threatening (an AE is considered “life-threatening” if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events (defined in paragraph below)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood disorders or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The Sponsor has a list of events that they classify as "always serious" events (***Section 12.4 Events Handled as Serious***). If an AE is reported that is considered to be an event per this classification as "always serious," the investigator will need to report this event as a SAE, even if it does not meet the above criteria.

5.5.3 Criteria for Causal Relationship to the Study Drug

AEs that fall under the categories of "Possible," "Probable," or "Not assessable" are defined as "AEs for which relationship to the study drugs could not be ruled out." For SAEs, AEs leading to discontinuation, and other AEs for which description of the basis for causality assessment is requested by the sponsor, the investigator/sub-investigator will enter the basis for the causality assessment on the eCRF.

Causal relationship to the study drug	Criteria for causal relationship
Not related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable temporal relationship to administration of the drug, but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).
Not assessable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

5.5.4 Criteria for Defining the Severity of an Adverse Event

The severity of each AE will be assessed and recorded on the eCRF, with reference to the "Criteria for Seriousness/Severity Grading of Adverse Drug Reactions" (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, dated June 29, 1992), or according to the following criteria for AEs not included in the above-mentioned document:

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of an SAE, the investigator or sub-investigator will report to the head of the study site and must contact the Sponsor or the CRO by telephone or fax immediately (within 24 hours of awareness).

The investigator will complete the "Serious Adverse Event Report Form" containing all information required by the regulatory authorities, and submit it to the Sponsor or CRO promptly (within 24 hours of becoming aware of the event) by fax, and also to the head of the hospital. If the faxing of the "Serious Adverse Event Report Form" is not possible or is not possible within 24 hours, the Sponsor or CRO should be informed by phone.

For contact details, see ***Section II Contact Details of Key Sponsor's Personnel***.

The "Serious Adverse Event Report Form" should be faxed to the following contact personnel:

Sponsor contact information:

[redacted] Astellas Pharma Inc.

Phone No.: [redacted]

Fax: [redacted]

Contract research organization (CRO) contact information:

[redacted]

Phone No.: [redacted] (Representative person)

Fax: [redacted]

5.5.6 Follow-up of Adverse Events

All AEs occurring during the study or before final observation are to be followed until they resolve or are judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

If during AE follow-up, the AE progresses to an "SAE," or if a subject experiences a new SAE, the investigator will immediately report the information to the Sponsor.

Even when the subject has not returned to normal or the level noted before administration of the study drug, if the investigator/sub-investigator judges that the follow-up of the subject is unnecessary or is completed and if the reason is appropriately specified in the source document, the follow-up may be unnecessary or completed.

5.5.7 Monitoring of Common Serious Adverse Events

Not applicable.

5.5.8 Procedure in Case of Pregnancy

If a female subject or male subject partner becomes pregnant during the study dosing period or within 28 days from the completion or discontinuation of study treatment, the investigator is to report the information to the Sponsor/CRO according to the procedures same as those for SAEs. This information should include the expected date of delivery, starting day of last menstruation, estimated conception date, pregnancy outcome, and neonatal data.

The investigator will follow-up the pregnancy in terms of the maternal and fetal medical conditions according to the same procedures as those for SAEs, and notify the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs (spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus]), the investigator should respond in accordance with the procedures for

SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion, and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator.
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth.
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.

5.5.9 Emergency Procedures and Management of Overdose

In the event of suspected overdose of gabapentin enacarbil, the subject should receive appropriate treatment and monitoring.

5.5.10 Supply of New Information Affecting the Conduct of the Study

1. When information is obtained regarding adverse drug reactions, etc., as specified in the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (PMD Act), the Sponsor should inform all the investigators involved in the clinical study, the head of each study site, and the regulatory authorities of such information in compliance with Article 80-2 Paragraph 6 of the PMD Act. The investigator will supply the new information to the subjects, in compliance with ***Section 8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent, and Revision of the Written Information***
2. In addition to the above item (1), when the head of the study site receives the revisions of the Investigator's Brochure, protocol, written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB, these documents should be sent to the IRB.

5.5.11 Deviations from the Protocol and Other Actions Taken to Avoid Life-Threatening Risks to Subjects

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol, in order to avoid urgent risks for subjects, the investigator should take the following actions:

1. Describe the contents of the deviation or amendment and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the Sponsor and the head of the study site. Keep a copy of the notice.

2. Consult with the Sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the Sponsor.

5.6 Test Drug Concentration

Not applicable.

5.7 Other Measurements, Assessments or Methods

All of the following data will be entered on the eCRF:

1) Pregnancy testing: Week −1 (run-in period), Week 12, discontinuation

Pregnancy testing (using a simple test kit on urine) will be performed before the start of the run-in period only in women, with the exception of women who are at least one year postmenopausal or with a history of hysterectomy, bilateral oophorectomy, etc., in whom a possibility of pregnancy is clearly excluded.

2) Estimated creatinine clearance: Week −1 (run-in period)

The estimated creatinine clearance is calculated using the Cockcroft-Gault equation, based on the creatinine level measured by laboratory testing. The age and body weight at the time of the creatinine measurement will be used for the calculation.

[Cockcroft-Gault equation]

$$\text{Estimated creatinine clearance (mL/min)} = \frac{[(140 - \text{Age}) \times \text{Body weight (kg)}]}{[72 \times \text{Serum creatinine}^{*}\text{(mg/dL)}]}$$

< For females, multiply by 0.85. >

*Serum creatinine by central measurement

5.8 Total Amount of Blood Collected

The schedule of blood sampling in this study and the total amount of blood collected in each subject are shown below. If follow-up laboratory tests are needed, additional blood sampling will be performed as needed, irrespective of this preplanned total amount of blood.

Amount of blood collected at a time:

	Week −1	Week 0	Week 2	Week 4	Week 8	Week 12	At discontinuation
Hematology tests	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL
Biochemistry tests	5 mL Including ferritin	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL
Thyroid function tests (TSH, Free T_4)		2 mL				2 mL	2 mL
Glucose	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL
HbA1c	2 mL						

Number of blood sampling time points: 6 times

Total amount of blood collected: 60 mL

6 DISCONTINUATION

6.1 Discontinuation of Individual Subjects

Discontinuation is defined as permanent withdrawal of enrolled subjects from the study, before completion of all protocol-specified procedures in the study.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the subject from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant (see ***Section 5.5.6 Follow-up of Adverse Events***).

Discontinuation Criteria from Treatment for Individual Subjects:

1. Adverse events
- Subject experiences an AE, and further participation in the study is judged to be difficult.
2. Lack of efficacy (Worsening of the target disease)
- Subject has insufficient improvement with the study drug, and is judged to require change of treatment.
- Subject has worsening of the target disease, and further participation in the study is judged to be difficult.
3. Withdrawal of consent
- Subject requests to withdraw from the study.
4. Lost to follow-up
- Subject changed residence or is referred to another clinic/hospital, or has other personal reasons such as busy schedule, which prevent further participation in the study

- Subject does not return to the study site (or lost contact with the study site)

5. Ineligibility (i.e., not fulfilling the inclusion criteria or meeting any of the exclusion criteria)

- Subject is found not to fulfil the inclusion criteria or to meet any of the exclusion criteria, on the basis of the results of tests or observations performed after the informed consent and before formal registration.

6. Protocol deviation

- Subject is found not to have met the inclusion/exclusion criteria, after formal registration as an eligible subject.
- Subject is found to have any other major deviation from the protocol.

7. Suicide

- Subject attempted suicide, or is judged by the investigator/sub-investigator to be at high risk for suicide.

8. Death

- Subject died (from any cause).

9. Pregnancy

- Female subject is found to be pregnant during the study period.

10. Other

- The investigator/sub-investigator judges that further study treatment is inappropriate in the subject, or the Sponsor requests to discontinue study treatment in the subject because of safety issues.

For the subjects discontinued after administration of the study drug for the treatment period, the tests/observations required at discontinuation (see ***Section V FLOW CHART AND SCHEDULE OF ASSESSMENTS***) will be promptly performed, and a post-treatment follow-up period will be provided as far as possible. For the subjects discontinued during the post-treatment follow-up period, the Week 13 procedures will be performed as the tests/observations at discontinuation.

For the subjects discontinued during the run-in period, the compliance status and any AEs will be investigated. Any AEs that are ongoing at the time of final observation will be followed (see ***Section 5.5.6 Follow-up of Adverse Events***).

For the subjects discontinued from the study, the investigator/sub-investigator should collect all study data up to the final observation.

For the subjects discontinued after administration of the study drug, the investigator/sub-investigator will specify the date of discontinuation and reason for the discontinuation on the eCRF. In addition, the investigator/sub-investigator should retain all study data from the discontinued subjects, and also enter these data on the eCRF and submit them to the Sponsor. For the patients withdrawn before the start of the run-in period, the reason for the withdrawal will be entered on the eCRF.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor and the head of the study site.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be performed by the statistician of the Sponsor. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings, and figures to be produced. The SAP will be finalized before the treatment code breaking. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

7.1 Sample Size

180 subjects per group (360 subjects in the two groups) as participants in the treatment period

[Rationale for the sample size]

The Japanese phase II/III study [CL-0003] demonstrated the change in IRLS score (mean and standard deviation) at the end of treatment period (Week 12) as shown in Table 8. Of the randomized subjects, 11.8% in the placebo group and 17.5% in the 600 mg group were discontinued during the treatment period.

Table 8: Change in IRLS score (mean and standard deviation) at the end of treatment period (i.e., Week 12 of study treatment) in the Japanese phase II/III study [CL-0003]: FAS

	Placebo		ASP8825 600 mg	
	N	**Mean (SD)**	**N**	**Mean (SD)**
Week 12 (LOCF)	116	−8.96 (7.286)	120	−11.10 (7.921)
Week 12 (Treatment period completers)	105	−9.27 (6.996)	98	−11.54 (7.793)

SD: Standard Deviation. LOCF: Last Observation Carried Forward

In addition, a repeated measures analysis of variance of the data from the patients given placebo or ASP8825 600 mg in the Japanese phase II/III study [CL-0003] and included in the

Full Analysis Set showed that the adjusted means of the change from baseline in IRLS score at the end of treatment period (Week 12) were −9.15 in the placebo group and −11.71 in the 600 mg group. The difference between the adjusted means from the two groups was −2.56.

On the basis of these results, the difference between treatment groups in the change from baseline in IRLS score at the end of treatment period (Week 12) as the primary endpoint of this study was assumed to be −2.56, with a standard deviation of 8.000 in both groups. Under these assumptions, to detect a statistically significant difference between gabapentin enacarbil and placebo using a 2-sample t-test with a two-sided significance level of 0.05 and a power of 80%, 155 subjects per group would be required. Assuming the discontinuation rate during the treatment period was approximately 15.0% in each group, the sample size has been set to 180 per group.

7.2 Analysis Sets

In principle, the analysis sets below will be used. However, the final decision on handling of cases for analyses will be made in a case review before the treatment code breaking, in light of opinions/advice from medical expert, statistical advisor, and others.

7.2.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all subjects who received the study drug for the treatment period and were evaluated for at least one efficacy (either primary or secondary) endpoint during the treatment period. The FAS will be the primary analysis set for efficacy analyses.

7.2.2 Per Protocol Set (PPS)

The Per Protocol Set (PPS) will consist of the subjects in the FAS who meet the following criteria:

- Subjects meeting the inclusion criteria
- Subjects not meeting any of the exclusion criteria that can affect efficacy assessments
- Subjects not using excluded concomitant medications or therapies that can affect efficacy assessments
- Subjects given the study drug for the treatment period for at least 2 weeks from the start of the treatment period
- Subjects with ≥ 70% compliance with study treatment during the treatment period

7.2.3 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) will consist of all subjects given at least one dose of the study drug for the treatment period.

7.3 Demographic and Baseline Characteristics

Using the FAS, PPS, and SAF, the subject demographic and other baseline characteristics will be summarized by treatment group. For continuous variables, the descriptive statistics will

include the number of subjects, mean, standard deviation, minimum, median, and maximum. For categorical variables, the descriptive statistics will include the frequency and proportion.

7.4 Analysis of Efficacy

The efficacy analyses below will be performed using the FAS as the primary analysis set. Unless otherwise stated, the analyses will be performed by treatment group.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

The primary efficacy endpoint is the change from baseline in IRLS score at the end of treatment period. Using a repeated measures analysis of variance model having the following average structure, the adjusted mean in each treatment group and its difference (gabapentin enacarbil group − placebo group) at the end of treatment period (Week 12) will be calculated, with comparison between the placebo group and the gabapentin enacarbil group:

Change in IRLS score at each time point

= IRLS score at baseline + Age category*[1] + Estimated creatinine clearance category*[2] + Treatment group + Time point + Treatment group × Time point

*[1]Age category: < 50 years and ≥ 50 years

*[2]Estimated creatinine clearance category: ≥ 60 to < 90 mL/min and ≥ 90 mL/min

Compound symmetry will be used as the covariance structure for repeated measures of the response variable. A two-sided significance level of 0.05 will be used for statistical tests.

7.4.1.2 Secondary Analysis

- The analysis stated in ***Section 7.4.1.1 Primary Analysis***, will be performed using the PPS.
- The sensitivity analysis of ***Section 7.4.1.1 Primary Analysis***, will be performed using analysis of covariance with LOCF or other approaches taking into account missing data mechanisms. Details of sensitivity analysis will be specified in the SAP.

7.4.2 Analysis of Secondary Endpoints

1. Change from baseline in IRLS score at each time point

- The measured value and its change from baseline will be summarized using descriptive statistics. Comparison between the placebo group and the gabapentin enacarbil group will be performed using analysis of covariance.
- For the measured value and its change from baseline, the mean ± standard deviation will be plotted.

2. ICGI responder rate at each time point

- The responder rate and its 95% confidence interval will be calculated. Comparison between the placebo group and the gabapentin enacarbil group will be performed using Fisher's exact test.
- The responder rate and its 95% confidence interval will be plotted.

3. PCGI responder rate at each time point
- The responder rate and its 95% confidence interval will be calculated. Comparison between the placebo group and the gabapentin enacarbil group will be performed using Fisher's exact test.
- The responder rate and its 95% confidence interval will be plotted.

4. Change from baseline in Pittsburgh Sleep Quality Index at each time point
- The measured value and its change from baseline will be summarized using descriptive statistics. Comparison between the placebo group and the gabapentin enacarbil group will be performed using analysis of covariance.
- For the measured value and its change from baseline, the mean ± standard deviation will be plotted.

5. Change from baseline in Athens Insomnia Scale each time point
- The measured value and its change from baseline will be summarized using descriptive statistics. Comparison between the placebo group and the gabapentin enacarbil group will be performed using analysis of covariance.
- For the measured value and its change from baseline, the mean ± standard deviation will be plotted.

6. Change from baseline in RLS Pain score at each time point
- The measured value and its change from baseline will be summarized using descriptive statistics. Comparison between the placebo group and the gabapentin enacarbil group will be performed using analysis of covariance.
- For the measured value and its change from baseline, the mean ± standard deviation will be plotted.

7. Change from baseline in EQ-5D-5L at each time point
- The measured value and its change from baseline will be summarized using descriptive statistics.

7.5 Analysis of Safety

Using the SAF, the following safety analyses will be performed by treatment group.

7.5.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The AEs, SAEs, AEs leading to discontinuation, and AEs related to the study drug will be summarized by System Organ Class, Preferred Term, and treatment group, with tabulation of the number and percentage of subjects. In addition, the number and percentage of subjects with AE will be tabulated by severity.

7.5.2 Laboratory Assessments

For laboratory test values (continuous values), the measured value and its change from baseline at each time point will be summarized using descriptive statistics. Shift tables will be constructed for the laboratory test values relative to the normal ranges from baseline to each time point during the treatment period. For discrete values, the frequency will be summarized for each time point.

7.5.3 Vital Signs

For vital signs, the measured value and its change from baseline at each time point will be summarized using descriptive statistics.

7.5.4 Body Weight

For body weight, the measured value and its change from baseline at each time point will be summarized using descriptive statistics.

7.5.5 Epworth Sleepiness Scale

For the Epworth Sleepiness Scale, the measured value and its change from baseline at each time point will be summarized using descriptive statistics.

7.6 Analysis of Pharmacokinetics

Not applicable.

7.7 Other Analyses

Not applicable.

7.8 Interim Analysis (and Early Discontinuation of the Study)

No interim analysis is planned.

7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Final decision on handling of missing data and outliers for analyses will be made before treatment code breaking, in light of opinions/advice from medical expert, statistical advisor, and others. In terms of the handling of data time points for analysis, if two or more observed

values are available for one time interval, the value collected closer to the protocol-specified time point will be used. If the difference from the reference time point is the same for two values, the value collected at a later point will be used.

7.9.1 IRLS score and RLS Pain score

For the IRLS score and the RLS Pain score, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

Analysis visit	Allowable time window	Reference day
Run-in	Day −10 to Day −7	Day 1
Week 0	Day 1	Day 1
Week 1	Day 5 to Day 11	Day 8
Week 2	Day 12 to Day 18	Day 15
Week 4	Day 26 to Day 32	Day 29
Week 6	Day 40 to Day 46	Day 43
Week 8	Day 54 to Day 60	Day 57
Week 10	Day 68 to Day 74	Day 71
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period
Follow-up	Reference day +5 days to Reference day +11 days	Day of last dosing in the treatment period

7.9.2 ICGI and PCGI

For the ICGI and PCGI, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

Analysis visit	Allowable time window	Reference day
Week 1	Day 5 to Day 11	Day 8
Week 2	Day 12 to Day 18	Day 15
Week 4	Day 26 to Day 32	Day 29
Week 8	Day 54 to Day 60	Day 57
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period
Follow-up	Reference day +5 days to Reference day +11 days	Day of last dosing in the treatment period

7.9.3 Pittsburgh Sleep Quality Index, Athens Insomnia Scale, and EQ-5D-5L

For the Pittsburgh Sleep Quality Index, Athens Insomnia Scale, and EQ-5D-5L, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

Analysis visit	Allowable time window	Reference day
Week 0	Day 1	Day 1
Week 4	Day 26 to Day 32	Day 29
Week 8	Day 54 to Day 60	Day 57
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period

7.9.4 Laboratory Tests

For laboratory tests, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

Analysis visit	Allowable time window	Reference day
Run-in	Day −10 to Day −7	Day 1
Week 0	Day 1	Day 1
Week 2	Day 12 to Day 18	Day 15
Week 4	Day 26 to Day 32	Day 29
Week 8	Day 54 to Day 60	Day 57
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period

7.9.5 Vital Signs

For the vital signs, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

Analysis visit	Allowable time window	Reference day
Run-in	Day −10 to Day −7	Day 1
Week 0	Day 1	Day 1
Week 1	Day 5 to Day 11	Day 8
Week 2	Day 12 to Day 18	Day 15
Week 4	Day 26 to Day 32	Day 29
Week 6	Day 40 to Day 46	Day 43
Week 8	Day 54 to Day 60	Day 57
Week 10	Day 68 to Day 74	Day 71
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period

7.9.6 Body Weight

For body weight, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

Analysis visit	Allowable time window	Reference day
Run-in	Day −10 to Day −7	Day 1
Week 0	Day 1	Day 1
Week 4	Day 26 to Day 32	Day 29
Week 8	Day 54 to Day 60	Day 57
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period

7.9.7 Epworth Sleepiness Scale

For the Epworth Sleepiness Scale, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

Analysis visit	Allowable time window	Reference day
Week 0	Day 1	Day 1
Week 1	Day 5 to Day 11	Day 8
Week 2	Day 12 to Day 18	Day 15
Week 4	Day 26 to Day 32	Day 29
Week 6	Day 40 to Day 46	Day 43
Week 8	Day 54 to Day 60	Day 57
Week 10	Day 68 to Day 74	Day 71
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period
Follow-up	Reference day +5 days to Reference day +11 days	Day of last dosing in the treatment period

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator, sub-investigator, or clinical research coordinator will enter data using an Electronic Data Capture (EDC) system. For efficient data collection, the investigator, sub-investigator, or clinical research coordinator should record data (including laboratory values, if applicable) on the eCRF within 5 days after the subject visit.

For questionnaires completed by subjects (i.e., PCGI, Pittsburgh Sleep Quality Index, Athens Insomnia Scale, RLS Pain score, EQ-5D-5L, and Epworth Sleepiness Scale), the investigator, sub-investigator, or clinical research coordinator will check the entries and enter these data into the eCRF. The subject will review the entries together with a clinical research coordinator after completing the questionnaires. If any entry is unclear, the subject will make an additional entry or correct the entry as necessary, and enter the date of the correction and sign or affix his or her personal seal.

The investigator, sub-investigator, or clinical research coordinator is responsible to ensure that all data on the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents will be appropriately maintained by the site.

The monitor should verify the data on the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests will be performed at a central laboratory. Central laboratory data will be transferred electronically from the central laboratory to the Sponsor at predefined times. The central laboratory will provide the Sponsor with a complete copy of the data.

For the patients withdrawn before the start of the run-in period, the date of informed consent, minimum patient background data (sex, date of birth), and reason for withdrawal will be entered on the eCRF.

For the patients withdrawn during the run-in period, the date of informed consent, patient background data (sex, date of birth, family history of RLS), visit days, date of provisional registration, date of final observation, any discontinuation of study drug, date of discontinuation, reason for discontinuation, date of run-in period study drug prescription, number of the study drugs prescribed, start and end date of study drug administration, number of the study drugs retrieved, number of the study drugs lost, AEs, and IRLS score will be entered on the eCRF.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (date of birth, sex, height, body weight)
- Inclusion and exclusion criteria-related detailed records
- Documentation of participation in the study and the original signed and dated informed consent form
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data
- AEs and symptomatic treatments
- Results of relevant examinations
- Laboratory printout
- Details of dispensing and return of study drug
- Reason for premature discontinuation
- Subject ID number
- Questionnaire forms (IRLS score, ICGI, PCGI, Pittsburgh Sleep Quality Index, Athens Insomnia Scale, RLS Pain score, EQ-5D-5L, Epworth Sleepiness Scale)

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to ***Section 8.1.2 Specification of Source Documents***) when they are requested by the Sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations, when the source documents are subject to direct access.

8.1.5 Data Management

Data management will be coordinated by the Data Science department of the Sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by the Data Management department. The methods for eCRF completion and correction will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and Iyakuhinmei Data File (IDF), respectively.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB)

Before the contract for the study is executed, the institutional review board of the study site will need to review and approve the study protocol and various materials used for the patient informed consent procedure, to protect human rights of the patients and secure the safety and welfare of the patients.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the contents of the study to the subjects using the written information, and answer all questions regarding this study. Prior to any study-related screening procedures being started in the subject, the subject should read through and fully understand the informed consent form and provide voluntary written consent to participate in the study. The consent form will be signed (or seal affixed with name) and dated by the investigator or his/her representative who provided the explanation (including a clinical research coordinator who provided supplementary explanation where applicable) and the subject. The investigator or his/her representative will provide the subject with a copy of the signed (or seal affixed with name) consent form, while retaining the original in the subject's source documents. The investigator will confirm that the original consent form was dated by the subject, and also confirm that the consent was obtained before

the study-related screening procedure and the subject received a copy of the signed consent form.

The investigator will retain the signed consent forms, and will have them available (for review only) to the study monitor, audit/inspection personnel of regulatory authorities, and other authorized persons upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent, and Revision of the Written Information

1. The investigator will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records, and whether the subject willing to remain in the study or not must be confirmed and documented.
2. The investigator must update the ICF and submit it for approval to the IRB/IEC. The investigator must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent subjects with the updated ICF even if relevant information was provided orally. The investigator who obtained the written informed consent (including a clinical research coordinator who provided supplementary explanation where applicable) and the subject should sign (or affix seal with name) and date the informed consent form. A copy of the signed (or seal affixed with name) informed consent form will be given to the subject and the original will be retained in the subject's medical record. The re-consent process should be documented in the subject's record.

8.2.4 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

All persons and organizations involved in this study shall pay utmost respect to protect privacy of the subjects, for example by prohibiting the use of personally identifiable information (e.g., name, address). The details of privacy protection should comply with laws and regulatory requirements (e.g., Privacy Protection Laws).

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the clinical study agreement.

After agreement between the investigator and the Sponsor, the investigator may submit a manuscript for publication.

8.3.2 Documents and Records Related to the Clinical Study

The Sponsor will provide the investigator and the study site with the following:

- Study protocol (and amendments where applicable)
- Package insert (and revisions where applicable)
- CRF and Serious Adverse Event Report Form
- Study drug with all necessary documents
- Study contract and memoranda

Before initiation of the study, the investigator and the study site will provide the Sponsor with the following:

- Written agreement on the protocol between the Sponsor and the investigator
- Curriculum Vitae of the investigator
- List of sub-investigators and clinical research coordinators
- Copy of the IRB approval of the protocol, protocol amendments (if applicable), and other study documents (including a member list and quality assurance documentation)
- Instructions provided and decisions made by the head of the study site
- Study contract and memoranda
- Laboratory normal values and ranges (if applicable) (including updates or revisions)

At the end of the study, the Sponsor will retrieve the following:

- Study-related documents
- Unused study drugs

The investigator will retain all study data (e.g., subject screening list, source data, CRFs, investigator's file) and related communications. These documents are to be kept on file for the appropriate term determined by the local regulation.

The records to be retained at the study sites are the ones listed as essential documents in GCP. These records shall be retained by either the head of the study site or a responsible record keeper designated by the head of the study site, until a notice issued by the Sponsor on completion of the retention period is received. These documents are also subject to direct access and should be provided upon request from the Sponsor or regulatory authorities.

The head of the study site will retain the essential documents that should be stored at the study site in an appropriate manner according to the rules of the study site. The document retention period will be until completion of re-review/reevaluation of the study drug.

The following are the major records to be retained at the study site:

1. Source documents (clinical data, documents, and records for preparing the eCRF)
   Hospital records, medical records, test records, memoranda, subject diary or check lists for evaluation, dosing records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files, study-related records kept at the pharmacy/laboratory/medical technical office, subject registration forms, laboratory test slips including central measurements, worksheets specified by the Sponsor, records by clinical coordinators, and records related to the clinical study selected from those verified in other department/hospital
2. Contracts, written informed consent forms, written information, and other documents or copies prepared by the study personnel
   Study request form (including a request for continuation/amendment), review request form, notice of study contract, study contract and memoranda, notification of study discontinuation/completion, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), CV of the investigator, list of sub-investigators, list of signatures and seal imprints (copy), and CRF (CD-R), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study by the head of the study site (Article 32-1, MHW Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a clinical study for which the period exceeds one year or the adequacy of continuously conducting the clinical study from which information on adverse drug reactions is obtained, and other documents obtained.
   An agreed-upon protocol (including amendments), package insert (including revisions), operational procedures for the investigator, materials and information supplied by the Sponsor (e.g., AE reports), matters reported by the investigator (e.g., protocol amendments, AE reports), IRB operational procedures, IRB member list, materials for IRB reviews (including continuous review), IRB review records (including continuous review), and IRB review result reports (including continuous review), etc.
4. Documents and records related to study drug management and other study-related tasks

Written procedure for study drug management, study drug inventory and accountability records, study drug receipt/retrieval forms, and concomitant medication prescription records

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments or revisions. Depending on the nature of the changes, approval of or notification to the IRB and regulatory authorities may be required. The changes will become effective only after the approval of the Sponsor, the investigator, and the IRB, followed by approval of the head of the study site.

8.3.4 Insurance of Subjects and Others

If a subject suffers any study-related injury, the Sponsor will compensate appropriately according to the severity and duration of the damage. However, if the injury was caused intentionally or was due to gross negligence by the study site, the Sponsor will discuss with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

1. If a subject incurs an injury as a result of participation in the clinical study, the study site should provide medical treatment and take other necessary measures, and notify the Sponsor of the injury.
2. When the subject has claimed or may claim compensation from the study site for the above study-related injury, the study site will immediately communicate the fact to the Sponsor. Both parties will work together towards compensation settlement.
3. The Sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.
4. The Sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

8.3.5 Signatory Investigator for Clinical Study Report

Not established.

9 QUALITY ASSURANCE

The Sponsor will prepare written standard operating procedures (SOPs), and establish and maintain a system for quality assurance and quality control systems, to ensure that the study is conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

The Sponsor or its designee may inspect or audit any or all study sites and facilities. The site audit will include verification of regulatory documents, CRFs, source documents, and other documents via direct access by the auditor.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC) | Data and Safety Monitoring Board (DSMB) | Monitoring Committee | Other Evaluation Committee(s)

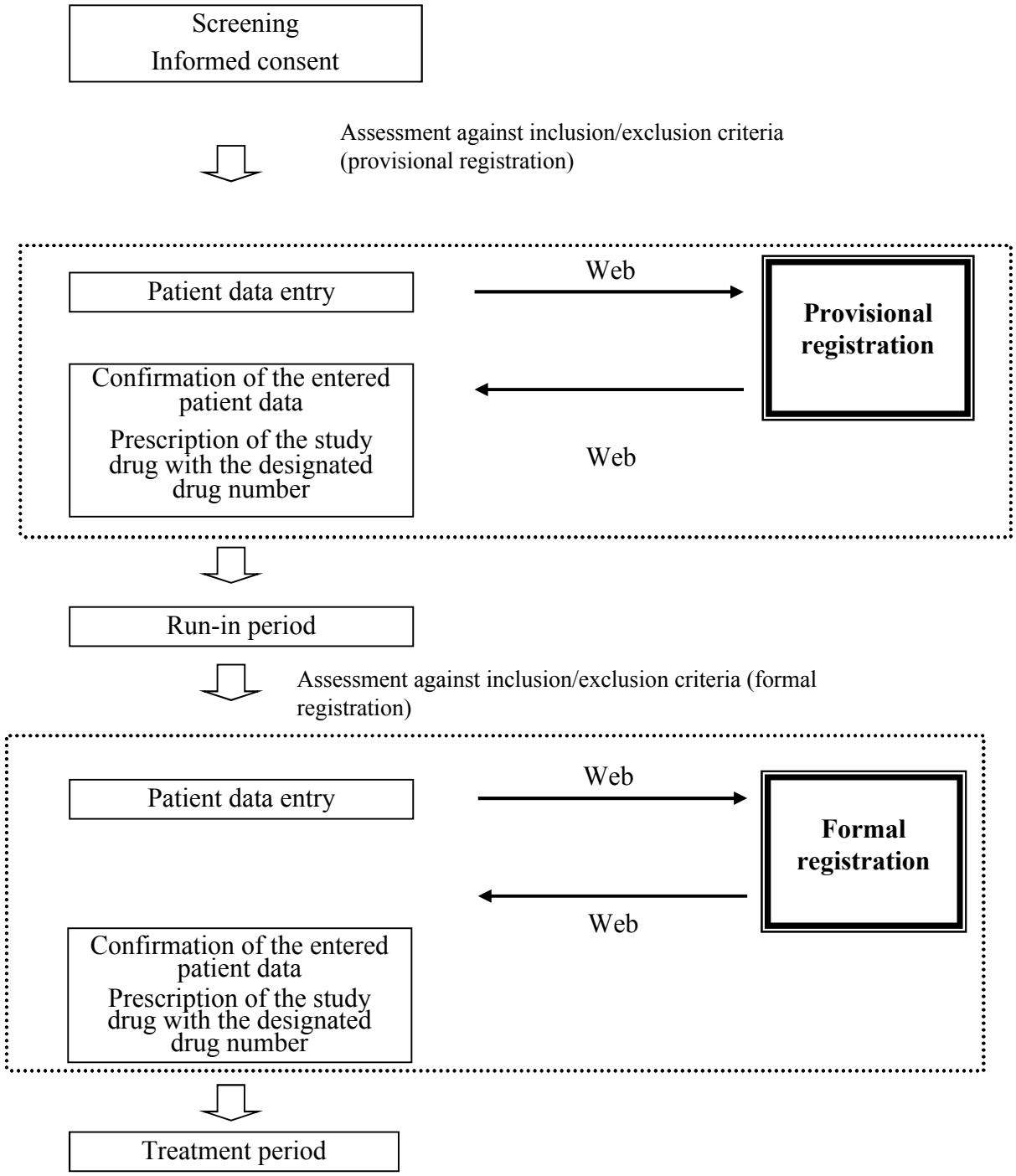
Not established.

10.2 Other Study Organizations

See Appendix 1 and Appendix 2.

10.3 Registration of Subjects

The procedures for subject registration will be defined in a separate written procedure or other documents.



Note) Also after the formal registration, the study drug with a drug number provided by the Web registration system will be prescribed on each occasion of study drug prescription.

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12 APPENDICES

12.1 List of Excluded Concomitant Medications

For excluded concomitant medications, a list of excluded concomitant medications, etc., will be provided separately.

12.2 Laboratory Tests

	Analyte	Visit	Test tube
Hematology tests	Red blood cell count (RBC) White blood cell count (WBC) White blood cell differential count Platelet count Hemoglobin Hematocrit MCV	Week −1 (run-in period), Week 0, Week 2, Week 4, Week 8, Week 12, discontinuation	EDTA-2K tube 2 mL
Biochemistry tests	Serum total protein (TP) Serum albumin (BCG assay) Total bilirubin ALP AST (GOT) ALT (GPT) Gamma-GTP Sodium (Na) Potassium (K) Calcium (Ca) Chloride (Cl) Inorganic phosphorus Serum creatinine Urea nitrogen Uric acid CPK	Week −1 (run-in period), Week 0, Week 2, Week 4, Week 8, Week 12, Discontinuation	Serum tube 5 mL[*1]
	Glucose	Week −1 (run-in period), Week 0, Week 2, Week 4, Week 8, Week 12, Discontinuation	Sodium fluoride (NaF) tube 2 mL
	HbA1c[*2]	Week −1 (run-in period)	EDTA-2K tube 2 mL
Immunology test	Ferritin[*2]	Week −1 (run-in period)	(Same as for biochemistry tests)
Thyroid function tests	TSH, Free T_4	Week 0, Week 12, Discontinuation	(Same as for biochemistry tests)
Urinalysis	Protein Glucose Urobilinogen	Week −1 (run-in period), Week 0, Week 2, Week 4, Week 8, Week 12, Discontinuation	Urine test tube

[*1] At Week 0, Week 12 or discontinuation, 7 mL will be drawn for measurements including TSH and free T4.

[*2] Ferritin and HbA1c are not handled as safety variables of this study.

12.3 Common Serious Adverse Events

Not applicable.

12.4 Events Handled as Serious

If any of the events listed below are noted during the study, they should be regarded as SAEs and reported in accordance with ***Section 5.5.5 Reporting of Serious Adverse Events (SAEs)***.

- Acute liver failure
- Acute renal failure
- Acute respiratory failure
- Agranulocytosis
- Anaphylaxis
- Any malignancy
- Aplastic anemia
- Confirmed or suspected transmission of infectious agents by marketed product)
- Congenital anomalies
- Hepatic necrosis
- Malignant hypertension
- Pulmonary hypertension
- Convulsion
- Torsades de pointes
- Toxic epidermal necrolysis
- Ventricular fibrillation
- Hemolytic anemia
- Bone marrow failure
- Myocardial infarction
- Cardiac arrest
- Deafness
- Blindness
- Pancreatitis acute
- Acute graft versus host disease
- Septic shock
- Sepsis
- Rhabdomyolysis
- Respiratory failure
- Stevens-Johnson syndrome

12.5 Criteria for Seriousness/Severity Grading of Adverse Drug Reactions (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, dated June 29, 1992)

Liver

Seriousness/severity of liver disorder is graded on the basis of the laboratory test values, symptoms, etc., shown in the table below, in principle. When liver disorder is suspected because of the presence of clinical symptoms such as general malaise, inappetence, nausea, pyrexia, and rash, laboratory data, including GOT and GPT, in the patient should be checked, and the table below should be used similarly for grading. Results of a liver biopsy, if available, should also be taken into account.

Grade of adverse drug reaction	Grade 1	Grade 2	Grade 3
Total bilirubin (mg/dL)	≥ 1.6, < 3.0	≥ 3.0, < 10	≥ 10
GOT, GPT (U)	≥ 1.25 × N, < 2.5 × N ≥ 50, < 100	≥ 2.5 × N, < 12 × N ≥ 100, < 500	≥ 12 × N ≥ 500
ALP	≥ 1.25 × N, < 2.5 × N	≥ 2.5 × N, < 5 × N	≥ 5 × N
γ-GTP	≥ 1.5 × N		
LDH	≥ 1.5 × N	_____	_____
PT[Note)]	_____	_____	≤ 40%
Symptoms, etc.	_____	Jaundice Hepatomegaly Pain in the right hypochondrium Hepatic steatosis	Bleeding tendency, disturbed consciousness, or other symptoms of hepatic failure (fulminant hepatitis) Hepatic cirrhosis Liver tumor Jaundice lasting ≥ 6 months

N: Upper normal limit of the institution

Note) prothrombin

Kidney

Seriousness/severity of renal disorder is graded on the basis of the laboratory test values, symptoms, etc., shown in the table below, in principle. When renal disorder is suspected because of the presence of clinical symptoms such as general malaise, inappetence, nausea, edema, hypertension, dull headache, and/or urine findings, the patient's BUN, creatinine, and other data will be checked, and the table below will be used similarly for grading. Results of a kidney biopsy, if available, should also be taken into account.

Grade of adverse drug reaction	**Grade 1**	**Grade 2**	**Grade 3**
BUN (mg/dL)	> 1 × N and < 25	≥ 25, < 40	≥ 40
Creatinine (mg/dL)	> 1 × N and < 2	≥ 2, < 4	≥ 4
Proteinuria	1 +	2 + or 3 +	> 3 +
Hematuria	Microscopic	Gross	Gross, blood clots
urine volume	———	≤ 500 mL/24hr, or oliguria/polyuria[Note)]	≤ 100 mL/24hr, or anuria
Serum potassium (mEq/l)	———	≥ 5.0, < 5.5	≥ 5.5
Other manifestations	———	———	Nephrotic syndrome Acute renal failure (interstitial nephritis, renal tubular necrosis, renal necrosis, renal papillary necrosis, renal cortical necrosis) Chronic renal failure (interstitial nephritis, renal tubular necrosis, renal necrosis, renal papillary necrosis, renal cortical necrosis) Uremia Hydronephrosis

N: Upper normal limit of the institution

Note) Nephrogenic diabetes insipidus.

Blood

Seriousness/severity of blood disorder is graded on the basis of the laboratory test values, symptoms, etc., shown in the table below, in principle.

Grade of adverse drug reaction	Grade 1	Grade 2	Grade 3
Red blood cells	< 3.5 million, ≥ 3 million	< 3 million, ≥ 2.5 million	< 2.5 million
Hb (g/dL)	< 11, ≥ 9.5	< 9.5, ≥ 8	< 8
White blood cells	< 4000, ≥ 3000	< 3000, ≥ 2000	< 2000
Granulocytes	< 2000, ≥ 1500	< 1500, ≥ 1000	< 1000
Platelets	< 100000, ≥ 75000	< 75000, ≥ 50000	< 50000
Bleeding tendency	Mild hemorrhage (Subcutaneous hemorrhage)	Moderate hemorrhage (Mucosal hemorrhage) Note 1)	Severe hemorrhage (Internal hemorrhage of organ) Note 2)
Other manifestations	———	———	Pancytopenia (e.g., aplastic anemia) Pure red cell aplasia Agranulocytosis

Note 1) Mucosal hemorrhage = gingival bleeding, epistaxis

Note 2) Internal hemorrhage of organ = intracranial hemorrhage, gastrointestinal hemorrhage, pulmonary hemorrhage, renal hemorrhage, genital hemorrhage, muscle hemorrhage, joint internal hemorrhage

Hypersensitivity symptoms

Seriousness/severity of hypersensitivity symptoms is graded on the basis of the manifestations shown in the table below, in principle.

<table>
<tr><th colspan="2">Grade of adverse drug reaction</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th></tr>
<tr><td colspan="2" rowspan="2">Cutaneous symptoms</td><td>Local rash (e.g., local erythema, papules)
Itching</td><td>Diffuse rash
(e.g., generalized erythema, purpura, blisters)</td><td rowspan="2">Oculomucocutaneous syndrome
Toxic epidermal necrolysis
Erythroderma (exfoliative dermatitis)
Weber-Christian disease
SLE-like symptoms[Note 1)]
Scleroderma
Pemphigoid lesions</td></tr>
<tr><td colspan="2">(e.g., photosensitivity, fixed eruption, erosions/ulcers, pigmentation)</td></tr>
<tr><td rowspan="4">Generalized symptoms</td><td>Pyrexia</td><td colspan="2">Pyrexia[Note 2)Note 3)]</td><td>———</td></tr>
<tr><td rowspan="2">Allergy</td><td>———</td><td>———</td><td>Shock
Anaphylactoid symptoms[Note 4)]</td></tr>
<tr><td colspan="2">Angioedema (face edema, eyelid edema, etc., except for laryngeal edema) [Note 3)]</td><td>Angioedema (Laryngeal edema)</td></tr>
<tr><td>Vasculitis</td><td>———</td><td colspan="2">Hypersensitivity vasculitis[Note 5)]</td></tr>
<tr><td colspan="2">Local symptoms</td><td colspan="2">Arthralgia[Note 3)]
Lymph node swelling[Note 3)]</td><td>———
———</td></tr>
</table>

Note 1) For SLE-like symptoms, generalized symptoms should also be taken into account.

Note 2) This pyrexia refers to so-called “drug fever.”

Note 3) Grade 1 or Grade 2 is determined at the discretion of the attending physician, etc.

Note 4) Anaphylactoid symptoms refer to either the onset of a combination of multiple generalized serious symptoms including dyspnea, generalized flushing, angioedema (e.g., face edema, laryngeal edema), or urticaria, or the onset of allergic-appearing acute serious dyspnea, without decrease in blood pressure.

Note 5) Grade 2 or Grade 3 is determined at the discretion of the attending physician, etc.

Respiratory system

Seriousness/severity of respiratory disorder is graded on the basis of the laboratory test values, symptoms, etc., shown in the table below, in principle.

Grade of adverse drug reaction		**Grade 1**	**Grade 2**	**Grade 3**
Respiratory state	Dyspnea	Shortness of breath HJ Class II[Note 1)]	Exertional dyspnea HJ Class III to IV[Note 1)]	Dyspnea at rest HJ Class V[Note 1)]
	Respiratory rhythm disorder	———	Transient hyperventilation Sleep apnea without clinical symptoms or hypoxemia[Note 2)]	Respiratory arrest (apnea) Respiratory depression (Hypoventilation, carbon dioxide narcosis) Persistent hyperventilation (respiratory distress, hyperpnoea) Cheyne-Stokes respiration Sleep apnea with clinical symptoms or hypoxemia [Note 2)]
Arterial blood partial pressure of oxygen PaO_2 (mmHg)		< 70, ≥ 60	< 60, ≥ 50	< 50 Decrease by 20 from baseline
Arterial blood partial pressure of carbon dioxide $PaCO_2$ (mmHg)		———	———	≥ 50 (Hypoventilation) ≤ 30 (Hyperventilation)
%VC FEV1.0%		——— ———	< 70%, ≥ 50% < 70%, ≥ 50%	< 50% < 50%
Chest X-ray findings	Infiltrative shadow	———	< 1/3 of one lung[Note 3)]	≥ 1/3 of one lung[Note 3)]
	Interstitial shadow	———	———	Diffuse interstitial shadow
	Pleural effusion	———	< 1/3of one lung[Note 3)]	≥ 1/3 of one lung[Note 3)]
Asthmatic attack		———	Wheezing, mild attacks[Note 4)]	Moderate attacks, severe attacks[Note 4)] Status asthmaticus
Hemoptysis		———	Bloody sputum	Hemoptysis
Other manifestations		Hiccups, yawning, hoarseness, sneezing, nasal congestion/intranasal abnormality, cough, increased sputum/ sputum excretion difficulty, laryngopharyngeal discomfort, throat pain, respiratory tract irritation, chest tightness	———	ARDS (adult respiratory distress syndrome), interstitial pneumonia, PIE syndrome, pulmonary fibrosis, hypersensitivity pneumonitis, pulmonary edema, pulmonary embolism, pulmonary vasculitis, glossoptosis, laryngospasm, glottis edema, pulmonary hypertension[Note 6)]
		Chest pain, laryngeal narrowing sensation (laryngopharyngeal abnormal sensation) [Note 5)]		

Note 1) Hugh-Jones (HJ) classification of dyspnea:

Class I = Able to walk and go up and down slopes and stairs similarly to healthy people of the same age. Has no shortness of breath.

Class II = Able to walk similarly to healthy persons of the same age, but unable to go up and down slopes and stairs.

Class III = Able to walk 1600 meters or more, though slower than healthy people of the same age

Class IV = Needs to stop for breath when walking 45 meters

Class V = Has shortness of breath when changing clothes or speaking, and is too breathless to leave home

Note 2) Sleep apnea refers to stopping of breathing for 10 seconds or longer, occurring approximately five times in one hour of sleep. Clinical symptoms include headache, erectile dysfunction, hypertension, cardiac failure, and excessive daytime lethargy.

Note 3) If no severity information is available regarding infiltrative shadow or pleural effusion, Grade 3 should be used.

Note 4) Asthmatic attacks are classified roughly as follows:

Mild attacks: Difficult to breathe, but able to lie down. Able to talk normally and move normally.

Moderate attacks: Unable to lie down because of difficulty breathing. Somewhat difficult to talk. Considerably difficult to move.

Severe attacks: Unable to move because of difficulty breathing. Difficult to talk. Unable to move.

For pediatric patients, the "Pediatric Allergy Study Group Severity Grading Committee Criteria" (see the next page) regarding the severity of pediatric bronchial asthma attacks should be referred to.

Note 5) Grade 1 or Grade 2 is determined at the discretion of the attending physician, etc.

Note 6) For severity of pulmonary arterial pressure, the seriousness/severity grading of pulmonary capillary pressure under the cardiovascular system should also be referred to.

(Reference) Pediatric Allergy Study Group Severity Grading Committee Criteria

Severity of pediatric bronchial asthma attacks

	Breathing status	**Living activities**			
		Playing	**Sleeping**	**Mood (Talking)**	**Eating**
Mild attack	Mild wheezing without dyspnea, possibly with slight intercostal retractions	Normal	Normal	Normal Talk normally	Normal
Moderate attack	Obvious wheezing and intercostal retractions with dyspnea	Somewhat difficult	Occasionally wake during sleep	Somewhat poor Able to talk back when talked to	Somewhat poor
Severe attack	Orthopnea with marked wheezing and dyspnea, orthopnea, possibly with cyanosis	Impossible or almost impossible	Impossible or almost impossible	Poor Unable to talk back even when talked to	Impossible or almost impossible

1. The severity of an attack should be assessed primarily on the basis of the breathing status, with supportive use of other items.
2. Decreased breath sounds and disturbed consciousness (e.g., excitement, decreased consciousness, decreased response to pain) are life-threatening signs.

Gastrointestinal system

Seriousness/severity of gastrointestinal disorder is graded on the basis of the laboratory test values, symptoms, etc., shown in the table below, in principle.

<table>
<tr><th colspan="2">Grade of adverse drug reaction</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th></tr>
<tr><td colspan="2">Nausea, Vomiting</td><td>Nausea (Queasy)</td><td>Vomiting[Note 1)]</td><td>_____</td></tr>
<tr><td colspan="2">Diarrhea</td><td>Soft stools, mushy stools</td><td>Watery stools not meting Grade 3</td><td>Watery stools with dehydration and electrolyte abnormality</td></tr>
<tr><td colspan="2">Gastrointestinal hemorrhage</td><td>Occult blood (+)</td><td>Bloody stools, hematemesis, or melena without any shock and decreased hemoglobin (≤ 8.0 g/dL)</td><td>Bloody stools, hematemesis, or melena with shock and decreased hemoglobin (≤ 8.0 g/dL)</td></tr>
<tr><td colspan="2" rowspan="3">Intraoral abnormality</td><td>Subjective intraoral discomfort
(Example) Lip dryness, intraoral discomfort, intraoral numbness, tasting bitter, tongue numbness, abnormal tongue feeling</td><td>Ulcerative stomatitis</td><td rowspan="3">_____</td></tr>
<tr><td colspan="2">Intraoral abnormality with objective inflammation, etc.[Note 1)]</td></tr>
<tr><td colspan="2">(Example) Angular stomatitis, cheilitis (lip vesicles), stomatitis (rough intraoral mucosa, gingival pain), glossitis (tongue eruption, rough tongue, glossodynia), coated tongue, black tongue, gingival hypertrophy</td></tr>
<tr><td colspan="2" rowspan="2">Esophageal abnormality</td><td>Subjective esophageal discomfort</td><td colspan="2">Esophageal abnormality with objective inflammation, ulcers, etc.[Note 2)]</td></tr>
<tr><td>(Example) Choking sensation, sensation of esophageal obstruction</td><td colspan="2">(Example) Esophagitis, esophageal ulcer</td></tr>
<tr><td>Dysphagia</td><td>_____</td><td>Swallowing difficulty</td><td>Swallowing inability</td></tr>
<tr><td rowspan="4">Gastrointestinal abnormality</td><td rowspan="2"></td><td>Subjective gastrointestinal discomfort
(Example) Heartburn, dyspepsia, heavy stomach feeling, stomach discomfort, abdominal discomfort, rumbling of the intestine, Inappetence</td><td>_____</td><td>_____</td></tr>
<tr><td>Pain</td><td>Pain in the stomach or abdominal not meeting Grade 2 which is tolerable or requires no treatment</td><td>Colic pain (stomach cramps, abdominal cramps, intestinal cramps)</td><td></td></tr>
<tr><td rowspan="3">Inflammation</td><td colspan="3">Gastritis, enterocolitis, colitis[Note 3)]</td></tr>
<tr><td colspan="2">Proctitis (rectal mucosal edema, rectal mucosal irritation) [Note 1)]</td><td>_____</td></tr>
<tr><td>_____</td><td colspan="2">Hemorrhagic colitis, pseudomembranous colitis[Note 2)]</td></tr>
</table>

<table>
<tr><th colspan="2">Grade of adverse drug reaction</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th></tr>
<tr><td rowspan="2">Gastrointestinal abnormality</td><td>Ulcer</td><td>Erosion</td><td>Gastric ulcer, duodenal ulcer, hemorrhagic ulcer, small intestine ulcer, large intestine ulcer[Note 2)]</td><td>Gastrointestinal perforation</td></tr>
<tr><td>Intestinal paralysis</td><td colspan="2">Constipation[Note 1)]</td><td>Ileus paralytic</td></tr>
<tr><td colspan="2" rowspan="3">Anal abnormality</td><td>Subjective anal discomfort
(Example) Anal pain, anal discomfort, anal distress, anal itching</td><td>—</td><td rowspan="3">—</td></tr>
<tr><td colspan="2">Anal abnormality with objective inflammation, etc. [Note 1)]
(Example) Periproctitis (anal roughness, anal erosion), hemorrhoidal hemorrhage, hemorrhoidal prolapse</td></tr>
<tr><td colspan="2">Pancreatic disorder</td><td>Abnormal amylase level only</td><td>Pancreatitis not meeting Grade 3</td><td>Pancreatic necrosis, hemorrhagic pancreatitis</td></tr>
<tr><td colspan="2" rowspan="2">Other manifestations</td><td>Hiccups, thirst (dry mouth), belching (eructation, burping), colon mucosal pigmentation, flatulence, flatus, sulfurous smell, frequent bowel movements (defecation desire, defecation urgency, tenesmus)</td><td>—</td><td rowspan="2">—</td></tr>
<tr><td colspan="2">Sialoadenitis, fecal incontinence[Note 1)]</td></tr>
</table>

Note 1) Grade 1 or Grade 2 is determined at the discretion of the attending physician, etc.

Note 2) Grade 2 or Grade 3 is determined on the basis of the severity of concurrent clinical symptoms such as diarrhea, gastrointestinal hemorrhage, and dysphagia.

Note 3) The terms gastritis, enterocolitis, and colitis are typically used when the patient has clinical symptoms such as vomiting, gastralgia, abdominal pain, diarrhea, irrespective of any presence of objective inflammation. Gastritis, enterocolitis, and colitis should thus be graded on the basis of the intensity of clinical symptoms such as vomiting.

Cardiovascular system

Seriousness/severity of cardiovascular disorder is graded on the basis of the laboratory test values, symptoms, etc., shown in the table below, in principle.

Grade of adverse drug reaction			Grade 1	Grade 2	Grade 3
Blood pressure abnormality	Decreased	Systolic blood pressure (mmHg)		< 90, ≥ 80	< 80
		Symptoms	Dizziness on standing up, orthostatic dizziness, orthostatic hypotension		No palpable pulse
	Increased		Increased blood pressure (abnormal increase in blood pressure, abrupt increase in blood pressure), hypertension		_____
Circulatory disorder			_____	_____	Shock, cyanosis, peripheral circulatory failure
Heart rate (bpm)	Tachycardia		_____	≥ 110, < 130	≥ 130
	Bradycardia		_____	< 50, ≥ 40	< 40
Arrhythmia			Palpitations, arrhythmia (without ECG measurements)		
			Supraventricular extrasystoles	Supraventricular tachycardia	
			Ventricular extrasystole (solitary)	Ventricular extrasystoles (two consecutive extrasystoles) Bigeminy	Ventricular extrasystoles (multifocal) (three or more consecutive extrasystoles), Ventricular tachycardia (six or more consecutive beats), Ventricular fibrillation, Torsades de pointes
				Atrial fibrillation (including paroxysmal) Atrial flutter	
				Tachycardia paroxysmal	
			First degree atrioventricular block (atrioventricular conduction time prolongation)	Second degree atrioventricular block, atrioventricular dissociation, sinus arrest, bundle branch block (intraventricular block) (defect conduction intraventricular), nodal rhythm, ventricular rhythm	Third degree atrioventricular block (complete atrioventricular block), cardiac arrest (cessation of heartbeat), Adams-Stokes syndrome
Electrocardiogram abnormal			P wave absent PR or PQ prolongation	ST elevation, ST depression, T wave inversion, T wave flattening, U wave appearance, QT prolongation, QRS widening	_____

Grade of adverse drug reaction		Grade 1	Grade 2	Grade 3
Cardiac failure-like symptoms			Edema (generalized, peripheral)	Cardiac failure (congestive cardiac failure), right cardiac failure, left cardiac failure (cardiac asthma), acute cardiac failure, cardiomegaly (increased cardiac ratio)
Reference	Myocardial contractility	60% ≥ left ventricular ejection fraction (LVEF) > 50%	50% ≥ LVEF >40%	40% ≥ LVEF
	Cardiac output (cardiac index)		2.5 l/min/m^2 ≥	2.2 l/min/m2 ≥
	Pulmonary capillary pressure (Pulmonary arterial systolic pressure) (mmHg)	≥ 20, < 30	≥ 30, < 40	≥ 40
	Dyspnea See the grading criteria in the Respiratory system section	Shortness of breath HJ Class II	Exertional dyspnea HJ Class III to IV	Dyspnea at rest HJ Class V
Ischemic heart disease-like symptoms		Chest discomfort Chest distressed feeling of Chest pressure		Worsening of angina pectoris Angina pectoris attack (induction) Myocardial infarction (coronary artery thrombosis) Myocardial necrosis
		Chest pain, anginal pain (angina-like pain), myocardial ischemia, coronary failure Note)		
Myocardial, pericardial, or endocardial disorder			Pericarditis Pericardial effusion Endocarditis	Myocarditis Myocardial fibrosis
		Myocardial disorder Note)		
Vascular disorder		Vascular pain	Angiospasm Intermittent claudication Arteriosclerosis	Gangrene Vasculitis Thrombophlebitis Thrombosis Arterial or venous thrombosis Thromboembolism Pulmonary embolism (Infarction) Cerebral embolism (Infarction) Mesenteric embolism
		Raynaud-like syndrome Note) (without gangrene)		
Other symptoms		Flushed face (hot flush) Feeling hot Burning sensation Face flush		

Note) Grade 1 or Grade 2 is determined at the discretion of the attending physician, etc.

Psychoneurological system

Seriousness/severity of psychoneurological disorder is graded on the basis of manifestations shown in the table below, in principle, taking into account of their nature such as whether subjective or objective, whether manageable or not, whether assistance is required or not, whether transient or persistent, and whether reversible or irreversible.

Grade of adverse drug reaction		Grade 1	Grade 2	Grade 3
Abnormal mental activities and behaviors	Hyperthymia or unstable mood	Subjective hyperthymia or unstable mood	Symptoms stated under Grade 1 are objectively notable, and accompanied by abnormal behaviors	Symptoms stated under Grade 2 are severe and uncontrollable
		(Example) Emotional instability, mood swings, labile affect, nervousness, irritable mood, irritability, bad mood, anxiety (feeling), feeling irritated, talkativeness, hyperthymia, cheerfulness, euphoria (euphoric mood)	(Example) Manic depression/Manic state, change to manic state, aggression, irritable excitation, excitement, irritability, unrest, irritable hyperkinesis, poriomania, impulsive behavior, lack of suppression, affective incontinence	
		Insomnia (sleep disorder)		
	Decreased mood/ volition/ behavior	Subjective decrease of mood/volition	Symptoms stated under Grade 1 are objectively notable	Symptoms stated under Grade 2 are severe and uncontrollable
		(Example) Hypobulia, dullness, lack of motivation, sensation of lack of motivation, listlessness, avolition, vague head, absent mindedness, dream-like state, decreased mental concentration, depressed state, depression (state), depressed mood, melancholia		(Example) Suicidal ideation/attempt, depressive stupor
	Psychosis-like symptoms	_____	Transient illusion/hallucination/delirium (e.g., nocturnal delirium)	Persistent illusion/hallucination/ delirium, confusion, delusion
	Cognitive disorder	Reduced subjective cognitive ability	Reduced objective cognitive ability	Symptoms stated under Grade 2 are severe and persistent
		(Example) Forgetfulness, decreased memory ability	(Example) Anterograde amnesia, retrograde amnesia	(Example) Dementia
Consciousness disorder		Subjective consciousness disorder	Objective consciousness disorder	Symptoms stated under Grade 2 are severe and persistent
		(Example) Arousal difficult, delayed awaking, feeling drunk, feeling of residual sleepiness after sleeping, sedation, excessive sedation, nightmare, excessive dreaming	(Example) Somnolence, lethargy, drowsiness, light-headedness state, clouding of consciousness, transient loss of consciousness, syncope, disturbed orientation, disorientation	(Example) Coma, persistent loss of consciousness
Movement disorder	Coordinated movement	Subjective impairment of coordinated movement	Objective impairment of coordinated movement	Symptoms stated under Grade 2 are severe and significantly interfere with activities of daily living, and require assistance
		(Example) light-headed feeling, dizziness, vertigo, swaying (feeling)	(Example) Ataxia, coordinated movement disorder	
	Gait	_____	Objective gait disturbance	Symptoms stated under Grade 2 are severe and significantly interfere with activities of daily living, and require assistance
			(Example) Frozen gait, gait disturbance, difficulty in walking, ataxic gait, abnormal gait	(Example) Abasia

Grade of adverse drug reaction			Grade 1	Grade 2	Grade 3
Movement disorder	Muscle strength/ Paralysis		———	Objective muscle strength decrease and impairment	Symptoms stated under Grade 2 are severe and significantly interfere with activities of daily living, and require assistance
				(Example) Hypotonia, muscle weakness, Muscular weakness, Paresis	(Example) Facial paralysis, quadriplegia, hemiplegia, monoplegia
	Myalgia/ Arthralgia		Symptoms tolerable or requiring no treatment	Severe and persistent symptoms	———
			(Example) Arthralgia, myalgia, back pain, low back pain, nuchal pain, neck pain		
	Extrapyramidal symptoms	Involuntary movement	Transient mild involuntary movements	Persistent involuntary movement that recognized as a neurological manifestation	Symptoms stated under Grade 2 are severe and significantly interfere with activities of daily living, and require assistance
			(Example) Transient tremor (limb tremor, finger tremor), hand tremor, tremor	(Example) Marked or persistent tremor, perioral involuntary movement, facial tic, protrusion tongue, mask-like face, dyskinesia, hyperkinesia, akathisia, hyperkinesis, Parkinson's syndrome (Parkinson symptoms, Parkinson-like symptoms, or their worsening)	
		Muscle tightness	Subjective muscle tightness abnormality	Severe muscle tightness recognized as a neurological manifestation	Symptoms stated under Grade 2 are severe and significantly interfere with activities of daily living, and require assistance
			(Example) Hypokinesia, slow movement, stiff shoulder, anteversion-anteflexion posture, a feeling of tension in lower limb	(Example) Facial or perioral tension, hypertonia, rigidity, muscle rigidity, myotonia, muscle stiffness, muscle spasticity, neck [limb] ankylosis, stiffness of body	
	Language disorder		Subjective language disorder	Objective language disorder	Symptoms stated under Grade 2 are severe and significantly interfere with activities of daily living, and require assistance
			(Example) Slurred speech due to impaired tongue (mouth) movement, tongue movement disturbance	(Example) Dyslalia, Dysarthria	(Example) Aphasia
	Eye movement disorder		———	Transient eye movement disorder (Example) Ocular deviation, oculogyric crisis, ocular lateral crisis, eyeballs raise upward, nystagmus, diplopia	Symptoms stated under Grade 2 are severe and persistent
	Reflex		Decreased reflex	Pathological increase of reflex	Appearance of pathological reflex
			(Example) Decreased tendon reflex, decreased reflex movement ability	Loss of reflex	(Example) Babinski reflex
Convulsion/Cramp			Subjective	Local cramp	Generalized convulsion
			(Example) Bodily shaking	(Example) Twitching, muscle twitching, head/facial spasm, upper limb extension, muscle cramps	(Example) Generalised convulsion, epileptic seizure, epilepsy-like seizure, clonic convulsion, tonic convulsion, seizure, induction of seizure, opisthotonos

Grade of adverse drug reaction		Grade 1	Grade 2	Grade 3
Sensory dysfunction	Auditory disorder	Subjective auditory disorder	Objective transient auditory disorder	Irreversible auditory disorder
		(Example) Tinnitus, ear congestion sensation	(Example) Decreased hearing, hypoacusis	(Example) Irreversible deafness, no hearing (total deafness)
	Visual disorder	Subjective visual disorder	Objective transient visual disorder	Irreversible visual disorder
		(Example) Photophobia, sensation of decreased visual acuity, visual flashes, blurred vision, visual accommodation disorder	(Example) Visual acuity reduced transiently, transient color blindness	(Example) Optic neuritis, blindness, visual field disorder
	Olfactory disorder	Transient smell disorder[Note)]		Irreversible smell disorder
		(Example) Dysosmia, strange smell sensation		(Example) Loss of smell
	Taste disorder	Transient taste disorder[Note)]		Irreversible taste disorder
		(Example) Tongue sensation abnormal, dysgeusia, hypogeusia		(Example) Loss of taste
	Perception (sensation) disorder	Transient perception (sensation) disorder[Note)]		Irreversible perception (sensation) disorder
		(Example) Limb numbness, tongue numbness, lip numbness, ear pain, perceptual (sensation) alteration, perceptual (tactile) loss		(Example) Loss of perception (sensation)
Peripheral nerve (nerve disorder)		Transient neuralgia	Persistent neuralgia	Symptoms stated under Grade 2 are severe and significantly interfere with activities of daily living, and require assistance
				(Example) Guillain-Barre syndrome, polyneuritis, peripheral neuritis, myopathy
Dependence			Slight psychological dependence, with a tendency toward dose increase (tendency toward drug tolerance)	Physical dependence, withdrawal symptoms (abstinence syndrome)
Other		Yawning, cerebral anemia-like of symptoms, floating sensation, unstable feeling, headache, heaviness of head (feeling), head pressure, strange sensation, abnormal physical feeling, fatigue, general malaise, feeling of weakness, discomfort, unpleasant feeling	Swallowing difficulty (decreased swallowing ability), salivation	Aphagia, neuroleptic malignant syndrome, malignant hyperthermia, encephalopathy/leukoencephalopathy, meningitis/meningitis-like symptoms, cerebrovascular disorders (e.g., cerebral hemorrhage, cerebral infarction)

Note) Grade 1 or Grade 2 is determined at the discretion of the attending physician, etc.

Metabolism and electrolyte abnormality

Seriousness/severity of metabolism or electrolyte abnormality is graded on the basis of the laboratory test values, symptoms, etc., shown in the table below, in principle.

Grade of adverse drug reaction		Grade 1	Grade 2	Grade 3
Blood glucose abnormality (mg/dL)	Increased blood glucose	Casual blood glucose 120–200 or Fasting 120–140 Postprandial 160–200	Casual blood glucose 201–300 or Fasting 141–200 Postprandial 201–300	Casual blood glucose ≥ 301
	Symptoms	———	———	Diabetic coma
	Decreased blood glucose	69–60	59–51	≤ 50
	Symptoms	———	Hypoglycemic symptoms such as dizziness, headache, hunger, irritated feeling, and marked sweating	Hypoglycemic coma, convulsion
Metabolic acidosis	Arterial blood pH	< 7.35, ≥ 7.20	< 7.20, ≥ 7.15	< 7.15
	Symptoms	———	———	Disturbed consciousness, decreased blood pressure, convulsion, respiratory disorder (Kussmaul breathing)
Metabolic alkalosis	Arterial blood pH	≥ 7.46, < 7.50	≥ 7.50, < 7.60	≥ 7.60
	Symptoms	———	———	Convulsion, tetany, hypertension, arrhythmia
Serum calcium abnormality (mg/dL)	Increased	≥ 10.6, < 12.1	≥ 12.1, < 15.0	≥ 15.0
	Symptoms	———	———	Disturbed consciousness
	Decreased	< 8.5, ≥ 8.0	< 8.0, ≥ 6.5	< 6.5
	Symptoms	———	———	Tetany, decreased blood pressure, arrhythmia, psychiatric symptoms
Serum potassium abnormality (mEq/l)	Increased[Note)]	≥ 5.0, < 5.5	≥ 5.5, < 6.0	≥ 6.0
	Symptoms	———	———	Arrhythmia, muscle paralysis
	Decreased	< 3.5, ≥ 3.1	< 3.1, ≥ 2.5	< 2.5
	Symptoms	———	———	Weakness, muscle paralysis, arrhythmia
Serum sodium abnormality (mEq/l)	Increased	≥ 150, < 155	≥ 155, < 160	≥ 160
	Symptoms	———	———	CNS symptoms (disturbed consciousness, convulsion)
	Decreased	< 135, ≥ 125	< 125, ≥ 115	< 115
	Symptoms	———	———	Psychiatric disorders, convulsion, disturbed consciousness, pathological reflex

12.6 International Restless Legs Syndrome Study Group Rating Scale (IRLS) (Investigator Version 2.2)

Ask the patient to rate his/her symptoms for the following ten questions. The patient, and not the examiner, should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions. The examiner should mark the patient's answers on the form.

In the past week

(1) Overall, how would you rate the RLS discomfort in your legs or arms?

[4]□ Very severe

[3]□ Severe

[2]□ Moderate

[1]□ Mild

[0]□ None

In the past week

(2) Overall, how would you rate the need to move around because of your RLS symptoms?

[4]□ Very severe

[3]□ Severe

[2]□ Moderate

[1]□ Mild

[0]□ None

In the past week

(3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?

[4]□ No relief

[3]□ Mild relief

[2]□ Moderate relief

[1]□ Either complete or almost complete relief

[0]□ No RLS symptoms to be relieved

In the past week

(4) How severe was your sleep disturbance due to your RLS symptoms?

[4]□ Very severe

[3]□ Severe

[2]□ Moderate

[1]□ Mild

[0]□ None

In the past week

(5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms?

[4]□ Very severe

[3]□ Severe

[2]□ Moderate

[1]□ Mild

[0]□ None

In the past week

(6) How severe was your RLS on the whole?

[4]□ Very severe

[3]□ Severe

[2]□ Moderate

[1]□ Mild

[0]□ None

In the past week

(7) How often did you get RLS symptoms?

[4]□ Very often (This means 6 to 7 days a week.)

[3]□ Often (This means 4 to 5 days a week.)

[2]□ Sometimes (This means 2 to 3 days a week.)

[1]□ Occasionally (This means 1 day a week or less.)

[0]□ Never

In the past week

(8) When you had RLS symptoms, how severe were they on average?

[4]□ Very severe (This means 8 hours or more per 24 hour day or more.)

[3]□ Severe (This means 3 to 8 hours per 24 hour day.)

[2]□ Moderate (This means 1 to 3 hours per 24 hour day.)

[1]□ Mild (This means less than 1 hour per 24 hour day.)

[0]□ None

In the past week

(9) Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school, or work life?

[4]□ Very severe

[3]□ Severe

[2]□ Moderate

[1]□ Mild

[0]□ None

In the past week

(10) How severe was your mood disturbance from your RLS symptoms–for example angry, depressed, sad, anxious, or irritable?

[4]□ Very severe

[3]□ Severe

[2]□ Moderate

[1]□ Mild

[0]□ None

(GPF 4.1J)