CLINICAL STUDY PROTOCOL

A Long-term Extension Study for the Phase 3 Study of Nalmefene (339-14-001) in Patients With Alcohol Dependence

(Phase 3 Trial)

NCT Number: 02382276

PRT NO. 339-14-002

PRT Version Date: 20 Nov 2014 （Version 2）

A Long-term Extension Study for the Phase 3 Study of Nalmefene (339-14-001) in Patients With Alcohol Dependence

(Phase 3 Trial)

Clinical Protocol

Protocol No.: 339-14-002

(Translated Version)

Confidential

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Version 1: 31 Oct 2014

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Statement of Confidentiality

The trial protocol is to be treated as confidential information and is to be made available only to persons involved in the trial. The content of the protocol is not to be disclosed to any third party without the prior written consent of Otsuka Pharmaceutical Co., Ltd., except in the case of its being explained to a candidate trial subject. Disclosure of the results of the trial to academic societies or journals, etc, in part or in whole, will require the prior written approval of Otsuka Pharmaceutical Co., Ltd.

Trial Protocol Synopsis

Name of Test Product	Lu AA36143 (international nonproprietary name [INN]: nalmefene; hereinafter referred to as "nalmefene")
Trial Title	A long-term extension study for the phase 3 study of nalmefene (339-14-001) in patients with alcohol dependence
Trial Objectives	The long-term safety and efficacy of nalmefene hydrochloride at 20 mg in patients with alcohol dependence will be evaluated in a multicenter, open-label, uncontrolled trial.
Phase of Development	Phase: 3 Type of trial: long-term safety trial
Trial Design	This trial will consist of a 24-week treatment period (open-label, uncontrolled), a 4-week run-out period (double-blind, placebo-controlled), and a 4-week posttreatment observation period. In the treatment period, subjects will receive nalmefene hydrochloride 20 mg. In the run-out period, subjects will be randomized to either nalmefene hydrochloride 20 mg group or placebo group at the ratio of 1:1, and will receive the corresponding investigational medicinal product (IMP).
Target Disease	Alcohol dependent patients
Target Number of Subjects	Approximately 400 subjects proceeding on from Study 399-14-001
Inclusion Criteria	1) Patients who have completed Study 339-14-001. 2) Patients who have signed the informed consent form (ICF) for Study 339-14-002.
Exclusion Criteria	Patients who fall under any of the following exclusion criteria at the examination at the end of the treatment period of Study 339-14-001 will be excluded from the trial. 1) The patient has a clinically significant unstable illness (eg, complication of New York Heart Association [NYHA] class III or IV heart failure or angina pectoris, renal function disorder with estimated glomerular filtration rate [eGFR] of < 30 mL/min/1.73 m^2, hepatic failure, and neoplastic disorder).

	2) The patient has a clinically significant abnormal electrocardiogram (ECG) which is inappropriate for the participation in the trial in the opinion of the investigator or subinvestigator. 3) The patient satisfies at least one of the following suicide risk criteria: • Answers "Yes" on the Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) and whose episode meeting criteria for any of these 2 C-SSRS Ideation Items occurred within the last 6 months, OR • Answers "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (Actual Attempt [non-fatal], Interrupted Attempt, Aborted Attempt, Preparatory Acts or Behavior, Completed Suicide) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, OR • The patient is, in the opinion of the investigator or subinvestigator, at significant risk of suicide. 4) The patient has at least one of the following laboratory findings: • Red blood cell count: $< 3{,}000{,}000/mm^3$, hemoglobin: < 9.5 g/dL, white blood cell count: $< 3{,}000/mm^3$, platelet count: $< 75{,}000/mm^3$ • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN) 5) The patient is mainly engaged in driving or those engaged in potentially hazardous activities, such as operating machinery or working in high place. 6) Women who are pregnant or breast-feeding, who may be pregnant, or who wish to become pregnant during the trial and within 4 weeks after the final IMP administration. Men whose partners wish to become pregnant during the trial and within 4 weeks after the final IMP administration. Also, patients who or whose partners cannot use birth control. 7) Patients otherwise judged by the investigator or

	subinvestigator to be inappropriate for inclusion in the trial for any reason.
Discontinuation Criteria	1) The subject requests to be withdrawn from the trial. 2) The subject experiences an adverse event (AE) making continuation of the trial difficult. 3) Psychosocial therapy other than BRENDA approach is needed (except for the period after the end of the examination of the run-out period). 4) The dose of the IMP needs to be changed. 5) It has been found after the start of the trial that the subject does not meet the inclusion criteria or falls under any of the exclusion criteria. 6) A female subject has become pregnant or been suspected of being pregnant. 7) The investigator or subinvestigator judges that the subject should be withdrawn for other reasons.
Investigational Medicinal Products, Dose and Regimen, and Treatment Period	IMP: White film-coated tablets containing 20 mg (as an anhydride of nalmefene hydrochloride) per tablet or placebo tablets. Dose and regimen: All subjects will receive one tablet of nalmefene hydrochloride 20 mg in the treatment period and one tablet of either nalmefene hydrochloride 20 mg or placebo in the run-out period. Each subject will be instructed to take one tablet (nalmefene hydrochloride 20 mg or placebo) on days when the subject perceives a risk of drinking alcohol, as needed 1 to 2 hours before the anticipated risk of drinking. If the subject has started drinking alcohol without taking the IMP, the subject should take one tablet as soon as possible. The IMP can be taken up to one tablet a day (one day is defined as the period from 0 AM of the day to 0 AM of the next day). Tablets must not be divided. Treatment period: 28 weeks (treatment period for 24 weeks and run-out period for 4 weeks)
Prohibited Concomitant Drugs and Restricted Concomitant Drugs	• Agents used for treatment of alcohol dependence • IMPs and drugs not approved in Japan • Opioid analgesics

	• Opioid antidiarrheal drugs • Antitussive drugs and cold medicines containing opioids • Antidepressants • Antipsychotics • Anticonvulsants • Anxiolytics • Hypnotics • Anorexics • Other psychotropic agents (including herbal agents used against mental disorder) • Antineoplastics • Muscle relaxants • Insulin • Anticoagulants • Antibiotics with possible interaction with alcohol (nitrofurantoin, metronidazole, and tinidazole) • Antifungal agents (systemic) • Steroids
Variables	Safety • Adverse events, clinical laboratory values, blood pressure and pulse rate, body weight, 12-lead ECG, physical examination, Profile of Mood States (POMS), C-SSRS, and dependency assessment Efficacy Baseline for the number of heavy drinking days (HDDs), total alcohol consumption (TAC), and drinking risk level (DRL) is defined as the data collected by the Timeline Followback (TLFB) method during the period of 4 weeks before the Screening Visit of Study 339-14-001. One month is defined as 4 weeks (28 days) for this trial. • Change in the number of HDDs from baseline (The number of HDDs is defined as the number of days per month [days/month] with alcohol consumption per day of > 60 g for males and > 40 g for females) • Change in TAC from baseline (TAC is defined as mean alcohol consumption per day

	[g/day] over a 1-month period) • Response Shift Drinking Risk Level (RSDRL): The percentage of subjects with a downward shift in DRL of 2 categories or more from baseline • Response Low Drinking Risk Level (RLDRL): The percentage of subjects with a low DRL or below • 70% TAC responder rate: The percentage of subjects whose TAC is reduced by ≥ 70% • HDD responder rate: The percentage of subjects in whom the number of HDDs is ≤ 4 • Clinical Global Impression-Severity of Illness (CGI-S) • Clinical Global Impression-Global Improvement (CGI-I) • MOS 36-item Short-form Health Survey (SF-36) • EuroQol 5 Dimension (EQ-5D) • Alcohol Quality of Life Scale (AQoLS) • Resource Use Measurement Questionnaire-Alcohol Dependence (RUMQ-ADP) • Gamma-glutamyl transferase (GGT) • ALT
Scheduled Duration of the Trial	05 Dec 2014 to 31 Mar 2018

Table of Contents

List of Abbreviations and Definition of Terms

List of Abbreviations

Abbreviation	Expansion
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AQoLS	Alcohol Quality of Life Scale
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{24h}	Area under the concentration-time curve from time zero to 24 hours
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
BAC	Breath alcohol concentration
BRENDA	Biopsychosocial evaluation, Report to the patient on assessment, Empathic understanding of the patient's situation, Needs collaboratively identified by the patient and treatment provider, Direct advice to the patient on how to meet those needs, Assess reaction of the patient to advice and adjust as necessary for best care
BUN	Blood urea nitrogen
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression-Global Improvement
CGI-S	Clinical Global Impression-Severity of Illness
CRF	Case report form
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DNA	Deoxyribonucleic acid
DRL	Drinking risk level
ECG	Electrocardiogram, electrocardiography
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	EuroQol 5 Dimension
FAS	Full analysis set
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HCG	Human chorionic gonadotropin
HDD	Heavy drinking day
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INN	International nonproprietary name
INR	International normalized ratio

Abbreviation	Expansion
IRB	Institutional review board
IVRS	Interactive voice response system
IWRS	Interactive web response system
MCV	Mean corpuscular volume
MMRM	Mixed model for repeated measures
NYHA	New York Heart Association
PCS	Potentially clinically significant
PET	Positron emission tomography
PK	Pharmacokinetic, pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
POMS	Profile of Mood States
PT	Preferred term
QTcB	QT interval as corrected by Bazett's formula
QTcF	QT interval as corrected by Fridericia's formula
RLDRL	Response Low Drinking Risk Level
RSDRL	Response Shift Drinking Risk Level
RUMQ-ADP	Resource Use Measurement Questionnaire-Alcohol Dependence
SF-36	MOS 36-item Short-form Health Survey
SOC	System organ class
SS	Safety set
TAC	Total alcohol consumption
TEAE	Treatment-emergent adverse event
TLFB	Timeline Followback
TMD	Total mood disturbance
ULN	Upper limit of normal
VAS	Visual analog scale

Definitions of Terms

Term	Definition
Screen failure	A screen failure is a subject from whom written informed consent was obtained, but who did not advance to the treatment period of this trial.
Individual subject trial start date	The day of obtaining the subject's written informed consent
Individual subject trial discontinuation date	The day when the investigator or subinvestigator determined that the subject was to be withdrawn from the trial or the day of the withdrawal examination, whichever is later
Individual subject trial completion date	The day of posttreatment observation examination (final observation day) or the date of trial discontinuation for the subject
Individual subject trial period	Period from the day of obtaining the subject's informed consent to the day of trial completion. Does not include the period of follow-up investigation of adverse events (AEs).

1 Introduction

1.1 Background of Trial Plan

Alcohol dependence is a psychiatric disorder characterized by cognitive, behavioral, and physiological symptoms in addition to continued alcohol consumption despite serious alcohol-related problems. The major symptoms of alcohol dependence include compulsive drinking behaviors, an increased tolerance to alcohol, and withdrawal symptoms associated with an elimination of alcohol in the body.[1] Many patients with alcohol dependence also suffer from physical complications such as liver disorders and cardiovascular disorders as well as psychiatric disorders such as depression and anxiety.[2,3] In addition, alcohol dependence is a serious social problem as it can be a cause of violent behaviors and traffic accidents by drinking driving. It has been reported that the number of the patients with alcohol dependence who are receiving any treatment in Japan is around 50,000 by the survey of Ministry of Health, Labour and Welfare in 2008.[4] On the other hand, the number of the patients with alcohol dependence was estimated to be 800,000 in accordance with International Classification of Diseases and Related Health Problems 10th Revision criteria by the survey conducted in 2003, indicating that large number of patients is dependent on alcohol.[5]

General treatment process for the patients with alcohol dependence in Japan consists of 1) introduction period to educate and motivate patients for disorder and treatment, 2) detoxification period to develop an appropriate response to acute intoxication and withdrawal symptoms, and 3) rehabilitation period to help continued abstinence.[6] In this process, the principal goal in the treatment of alcohol dependence was abstinence. In contrast, a new treatment strategy which incorporates the means of harm reduction[7] has been proposed in order to alleviate physical and psychological complications by the reduction of alcohol consumption in addition to abstinence-oriented therapy in foreign countries.[8] Like other countries, when abstinence is set as the sole goal, some alcohol-dependent patients refuse treatment and some cannot continue the treatment before achieving abstinence, which is a clinical problem in Japan. Thus, a new treatment strategy aiming at a reduction of alcohol consumption has recently been proposed in Japan.[9,10]

Nalmefene (clinical trial ingredient code: Lu AA36143; international nonproprietary name [INN]: nalmefene) is an opioid receptor antagonist synthesized at Rockefeller University, USA in the 1960s. Nalmefene selectively binds to opioid receptors, exerting

antagonist activity at the μ-opioid and δ-opioid receptors but partial agonist activity at the κ-opioid receptor. It is known that endorphin, an intrinsic opioid, is associated with the reinforcing effects of alcohol. Nalmefene is considered to decrease the reinforcing effects by counteracting the intrinsic opioid and reduce the alcohol consumption.[11,12] Nalmefene showed a reduction in voluntary alcohol consumption in pharmacological studies using rodents. H. Lundbeck A/S conducted clinical development of nalmefene in the EU and gained approval for marketing nalmefene hydrochloride 20 mg as a drug to be taken as needed for reducing alcohol consumption in alcohol-dependent patients in February 2013.[13]

Currently, alcohol-deterrent drugs (cyanamide and disulfiram) and a drug to help maintain alcohol abstinence (acamprosate calcium) are approved in Japan for the treatment of alcohol dependence. However, there are no drugs approved with an indication of a reduction of alcohol consumption. Based on the above background, Otsuka Pharmaceutical concluded that nalmefene, which possesses a new mechanism of action and is expected to be effective in reducing alcohol consumption, could significantly contribute to the medical treatment of alcohol dependence and began clinical development of nalmefene in Japan by entering into a contract for co-development with H. Lundbeck A/S in October 2013.

1.2 Study Results and Trial Rationale

1.2.1 Nonclinical Study Results

Nalmefene had high affinity to all opioid receptor subtypes in vitro, exerting antagonist activity at the μ-opioid and δ-opioid receptors but partial agonist activity at the κ-opioid receptor. No significant binding to other receptors, ion-channels and enzymes was observed. Nalmefene had opioid antagonistic properties in the rat tail flick test and tail skin temperature response in rats. In alcohol-preferring rats, concomitant administration of nalmefene reduces voluntary ethanol drinking.

Single and repeated-dose toxicity studies, mutagenicity tests and carcinogenicity bioassays, reproduction and developmental toxicology, local tolerance studies and dependence tests were conducted.

Safety pharmacological studies in animals showed no potential for interaction with the respiratory or cardiovascular systems, including the electrical conduction in the heart, at clinically relevant exposure levels. There were behavioral changes with dose-related effect in rats at doses above 50 mg/kg (passivity, dispersion in cage, increased touch

response and catalepsy). In single-dose acute toxicity studies in mice, rats, and rabbits severe toxicity (ataxia, convulsions) and deaths was induced in each species. The minimal lethal dose after single oral dosing was 200 mg/kg in mice, 250 mg/kg in rats, and 225 mg/kg in rabbits. Repeated-dose toxicity studies induced central nervous system toxicity (tremors, convulsions) and deaths in rats and dogs. No other definable toxicological findings were seen in either species although multiple hematological, clinical pathological, and organ weight changes were recorded. There were no histopathological findings considered to be treatment-related in rats and dogs.

Nalmefene did not affect male or female fertility in rats and was not associated with fetal malformations or affected fetal viability in rats or rabbits and post natal development in rats. A slight retardation in fetal development was noted in rabbit litters in terms of decreased ossification of the distal femur and reduced fetal weight at 200 mg/kg/day. Nalmefene has no genotoxic potential in a battery of in vitro and in vivo mutagenicity tests. No carcinogenic potential was observed in the 104-week rat study. The 80-week mouse carcinogenicity study was also negative. In dependence study, nalmefene has been found to be free of any actions likely to result in drug abuse in primates.

1.2.2 Clinical Study Results

Several clinical studies have been conducted overseas until now. This section reports results of a positron emission tomography (PET) study in healthy Caucasian subjects (Study CPH-101-0902), pharmacokinetics (PK) and safety results of a phase 1 study in healthy Japanese subjects (Study 13505A), and the results of 3 phase 3 studies in patients with alcohol dependence (Studies 12014A, 12023A, and 12013A).

1.2.2.1 Results of PET Study in Healthy Caucasian Subjects (Study CPH-101-0902)

A PET study in healthy Caucasian male subjects was conducted to investigate μ-opioid receptor occupancy in the brain region following single and once-daily 7-day repeated administration of nalmefene hydrochloride 20 mg. As a result, μ-opioid receptor occupancy by nalmefene hydrochloride 20 mg reached 94% to 100% at 3 hours after administration and remained at 83% to 100% until 26 hours after administration. Thus, it was shown that the maximal μ-opioid receptor occupancy rate (100%) can be achieved at 20 mg.

1.2.2.2 Results of Phase 1 Study in Healthy Japanese Subjects (Study 13505A)

Study 13505A consisted of Parts A and B. In Part A conducted in a randomized, open-label, 2-period crossover manner, 13 healthy Japanese males received a single oral dose of nalmefene hydrochloride at 20 mg under a fasted or fed condition to investigate food effect, safety, and tolerability. In Part B conducted in a randomized, double-blind, placebo-controlled, parallel-group manner, 81 healthy subjects consisting of 21 male and 20 female Japanese and 20 male and 20 female Caucasians received 5-day repeated oral doses of nalmefene hydrochloride at 20 and 40 mg to investigate PK, safety, and tolerability.

In Part A, when nalmefene hydrochloride 20 mg was orally administered under a fasted condition, the plasma nalmefene concentration reached the highest (27.0 ng/mL) approximately 1.5 hours after the administration, with a mean area under the concentration-time curve from time zero to infinity (AUC_{∞}) of 159 ng·h/mL and half-life of 12.2 hours. Under a fed condition, the plasma concentration reached the highest (25.4 ng/mL) approximately 1 hour after the administration, with a mean AUC_{∞} of 156 ng·h/mL and half-life of 12.3 hours. No influence of food on the PK of nalmefene hydrochloride was found. In Part B, in which when 20 mg was administered to Japanese male and female subjects, the plasma concentration reached the highest (30.8 ng/mL and 37.6 ng/mL) approximately 1 hour and 0.5 hour after the administration on Day 1, respectively, with a mean area under the concentration-time curve from time zero to 24 hours (AUC_{24h}) of 137 ng·h/mL and 140 ng·h/mL, respectively. On Day 5, the plasma concentration reached the highest (44.1 ng/mL and 53.4 ng/mL) approximately 0.5 hour after the administration both in male and female subjects, with a mean AUC_{24h} of 187 ng·h/mL and 186 ng·h/mL, respectively, and half-life of 11.2 hours and 11.1 hours, respectively. The maximum (peak) plasma concentration of the drug (C_{max}) and AUC_{24h} were slightly higher on Day 5 than on Day 1, but clinically significant accumulation was not observed. Exposure (area under the concentration-time curve [AUC] and C_{max}) was slightly higher in Japanese subjects than in Caucasian subjects, but there were no clinically significant differences between the races.

Major adverse events (AEs) (reported in at least 2 subjects) were fatigue, dizziness, and back pain in Part A and fatigue, dizziness, nausea, headache, back pain, euphoric mood, decreased appetite, nasopharyngitis, oropharyngeal pain, apathy, and hyperhidrosis in Part B. In both parts, most of these AEs were mild in severity. In Part A, one Japanese male

subject withdrew from the trial due to bacterial infection, whereas in Part B, one Japanese male subject withdrew from the trial due to dizziness, fatigue, and nausea that occurred after the administration of nalmefene hydrochloride 20 mg, and one Caucasian male withdrew due to anemia (prior to investigational medicinal product [IMP] administration). No serious AEs were reported in either part. In addition, there were no clinically significant changes in blood pressure, pulse rate, electrocardiogram (ECG) parameters, physical examinations, or clinical laboratory safety assessments. The safety and tolerability profiles in Japanese subjects were similar to those in Caucasian subjects.

Based on the results of the phase 1 study in healthy Japanese subjects mentioned above, nalmefene hydrochloride at 20 mg and 40 mg is considered to have no major safety concerns in Japanese subjects.

1.2.2.3 Results of Phase 3 Studies in Patients With Alcohol Dependence

Among three phase 3 studies, Study 12014A and Study 12023A were conducted to evaluate the efficacy of nalmefene hydrochloride 20 mg as-needed use for 24 weeks (hereinafter referred to as foreign phase 3 confirmatory studies) and Study 12013A was conducted to evaluate the safety of nalmefene hydrochloride 20 mg as-needed use for one year (hereinafter referred to as foreign phase 3 extension study). One-year efficacy results were described for Study 12013A.

1.2.2.3.1 Results of Foreign Phase 3 Confirmatory Studies (Studies 12014A and 12023A)

Two foreign phase 3 confirmatory studies with the same design were conducted by H. Lundbeck A/S in separate areas in EU. These foreign phase 3 confirmatory studies were conducted in patients with alcohol dependence[a] who had at least medium drinking risk level[3] (DRL) as randomized, double-blind, placebo-controlled, parallel-group comparative study to evaluate the efficacy and safety of oral nalmefene hydrochloride 20 mg as-needed use for 24 weeks.

In both studies, the number of heavy drinking days (HDDs) and total alcohol consumption (TAC) were the co-primary efficacy endpoints. In Study 12014A, nalmefene hydrochloride 20 mg was significantly superior to placebo in change in the number of HDDs and change in TAC from baseline until 24 weeks after start of

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[a]In the foreign phase 3 studies, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision was adopted for diagnostic criteria for alcohol dependence.

administration. In Study 12023A, nalmefene was superior to placebo in the change in the number of HDDs, but the reduction in TAC by nalmefene was not statistically significant compared with placebo.

These two studies were conducted in patients including those who had medium DRL. According to the European Medicines Agency (EMA) guideline on the development of medicinal products for the treatment of alcohol dependence,[14] patients enrolled in alcohol reduction studies should have a high or very high DRL. Furthermore, since a large reduction in alcohol consumption was observed in the observation period before randomization, there were many patients with improved DRL prior to therapeutic intervention in these studies. Thus, H. Lundbeck A/S conducted a post hoc analysis of the primary efficacy outcome in patient population in accordance with above-mentioned EMA guideline and whose alcohol consumption was not improved before the therapeutic intervention (ie, who had high or very high DRL at both screening and randomization). As a result, a statistically significant difference in favor of nalmefene in the change of the number of HDDs and TAC compared to placebo was observed in both Studies 12014A and 12023A ($p < 0.05$).

Nalmefene was administered to 302 and 341 subjects in Study 12014A and Study 12023A (described in the same order hereinafter), respectively, and placebo to 296 and 337 subjects, respectively. The incidences of AEs in the nalmefene hydrochloride group were 81% and 68%, respectively, and those in the placebo group were 67% and 59%, respectively. Most of AEs were either mild or moderate in severity. Withdrawal from the study due to AEs occurred in 23% and 7% in the nalmefene hydrochloride group, respectively, and 7% and 6% in the placebo group, respectively. Serious AEs occurred in 6% and 2% in the nalmefene hydrochloride group, respectively, and 5% and 3% in the placebo group, respectively. The most commonly reported treatment-emergent adverse events (TEAEs) in the nalmefene hydrochloride group that occurred with an incidence $\geq$ 5% and more than twice higher than placebo during the treatment period were dizziness, nausea, fatigue, sleep disorder, insomnia, vomiting, and hyperhidrosis in Study 12014A and nausea, dizziness, insomnia, and vomiting in Study 12023A. The changes in clinical laboratory values during the treatment period were similar between the nalmefene hydrochloride group and placebo group in both studies, and most of the values were within normal range. No clinically significant changes were observed in blood pressure, pulse rate, body weight, 12-lead ECG parameters, and Profile of Mood States (POMS) score in either study.

1.2.2.3.2 Results of Foreign Phase 3 Extension Study (Study 12013A)

Study 12013A was conducted in patients with alcohol dependence who had at least low DRL as randomized, double-blind, placebo-controlled, parallel-group comparative study to evaluate the safety and efficacy of oral nalmefene hydrochloride 20 mg as-needed use for 1 year.

In Study 12013A, statistically significant differences in the change in the number of HDDs and in TAC at 52 Week from baseline compared with placebo were seen ($p < 0.05$). In addition, statistically significant differences were also observed in the patients with high or very high DRL at both baseline and randomization.

Nalmefene was administered to 501 subjects, and placebo to 164 subjects. The incidence of AEs was 75% in the nalmefene hydrochloride group and 63% in the placebo group. Withdrawal due to AEs occurred in 11% in the nalmefene hydrochloride group and 3% in the placebo group. Serious AEs occurred in 7% in the nalmefene hydrochloride group and 5% in the placebo group. The most commonly reported TEAEs (reported in ≥ 5% and more than twice higher than that in the placebo group) in the nalmefene hydrochloride group during the treatment period were nausea, insomnia, dizziness, vomiting, fatigue, and decreased appetite.

Adverse events which occurred beyond 6 months after randomization were reviewed in order to evaluate AEs under long-term treatment. The numbers of patients receiving treatment for 6 months or longer were 388 and 133 in the nalmefene hydrochloride group and placebo group, respectively. The incidences of AEs under long-term treatment were 43% and 40.5% in the nalmefene hydrochloride group and placebo group, respectively. The incidences of the most commonly reported AEs in the nalmefene hydrochloride group (nausea, insomnia, dizziness, vomiting, fatigue, and decreased appetite) were < 5% under long-term treatment. The AEs which occurred with an incidence ≥ 5% in either nalmefene hydrochloride group or placebo group included nasopharyngitis (4.9% in the nalmefene hydrochloride group and 9.9% in the placebo group, described in the same order hereinafter), headache (5.9% and 5.3%), and insomnia (4.6% and 5.3%).

In this study, changes in clinical laboratory values during the treatment period were similar between the nalmefene hydrochloride group and placebo group, and most of the values were within normal range. No clinically significant changes were observed in blood pressure, pulse rate, weight, 12-lead ECG parameters, and POMS score in this study.

As mentioned above, no significant safety concerns with long-term administration of nalmefene hydrochloride were suggested in the clinical study conducted overseas.

1.2.3 Trial Rationale

Nonclinical studies of nalmefene hydrochloride required for the conduct of the proposed clinical trial have already been completed overseas. The efficacy of nalmefene hydrochloride 20 mg has been verified in multiple clinical trials in patients with alcohol dependence, and nalmefene hydrochloride 20 mg is approved in Europe. Prior to this trial, Study 339-14-001 is planned in order to verify the efficacy of nalmefene hydrochloride 20 mg and to collect information on dose response. While the treatment duration in Study 339-14-001 is 24 weeks, we deemed it necessary to accumulate safety data on 1-year treatment, considering the possibility that nalmefene is administered for a long term in the clinical settings. The duration of IMP treatment of this trial will be 28 weeks (treatment period plus run-out period). When combined with the preceding Study 339-14-001, the maximum duration of IMP treatment will be 52 weeks. Also, results of the phase 1 study in healthy Japanese subjects (Study 13505A) showed that the safety and tolerability profiles in Japanese subjects were similar to those in Caucasian subjects with no clinically significant difference between races although the exposure to nalmefene hydrochloride 20 mg tended to be slightly higher in Japanese subjects than Caucasian subjects. The dose of nalmefene hydrochloride in this extension study is set at 20 mg, the highest dose in the preceding Study 339-14-001. Thus, this clinical trial was planned in order to investigate long-term safety of nalmefene hydrochloride 20 mg.

Prior to the conduct of the present clinical trial, we had “Consultations after End of phase 2 study for drugs (other than orphan drug)” with the Pharmaceuticals and Medical Devices Agency (PMDA) on 16 May 2013 and 11 Jul 2014. After receiving advice for this trial from the PMDA, we reflected it in the trial protocol.

See the investigator’s brochure for further details of data mentioned in this protocol and other trial results.

2 Trial Objectives

The long-term safety and efficacy of nalmefene hydrochloride at 20 mg in patients with alcohol dependence will be evaluated in a multicenter, open-label, uncontrolled trial.

3 Trial Plan

3.1 Trial Design

This trial is intended to evaluate the long-term safety of nalmefene hydrochloride at 20 mg in patients with alcohol dependence who have completed Study 339-14-001. The outline of the trial design is shown in Figure 3.1-1.

This trial will consist of 1) a 24-week treatment period (open-label, uncontrolled), 2) a 4-week run-out period (double-blind, placebo-controlled), and 3) a 4-week posttreatment observation period. The duration of IMP treatment of this trial will be 28 weeks (treatment period plus run-out period). When combined with the preceding Study 339-14-001, the maximum duration of IMP treatment will be 52 weeks.

The investigator or subinvestigator will fully explain the details of this trial and obtain written informed consent from each subject by the end of the treatment period of Study 339-14-001.

In the treatment period, nalmefene hydrochloride will be administered at 20 mg. Each subject will be instructed to take the IMP orally on days when the subject perceives a risk of drinking alcohol, as needed 1 to 2 hours prior to the anticipated risk of drinking. The IMP can be taken up to one tablet a day (one day is defined as the period from 0 AM of the day to 0 AM of the next day), and if a subject requires dose change during the treatment period, the subject will be withdrawn from the trial. When a subject is withdrawn from the trial, the subject will be requested to visit the site and to undergo the specified assessments and examinations wherever possible.

In the run-out period, subjects will be randomized to either nalmefene hydrochloride 20 mg group or placebo group at 1:1 ratio. Each subject will be instructed to take the IMP orally on days when the subject perceives a risk of drinking alcohol, as needed 1 to 2 hours prior to the anticipated risk of drinking. The IMP can be taken up to one tablet a day (one day is defined as the period from 0 AM of the day to 0 AM of the next day), and if a subject requires dose change during the run-out period, the subject will be withdrawn from the trial. When a subject is withdrawn from the trial, the subject will be requested to visit the site and to undergo the specified assessments and examinations wherever possible.

A posttreatment observation period will be scheduled after the end of the run-out period to evaluate safety after the end of treatment with nalmefene hydrochloride. However,

posttreatment observation will be performed only in subjects who complete the run-out period.

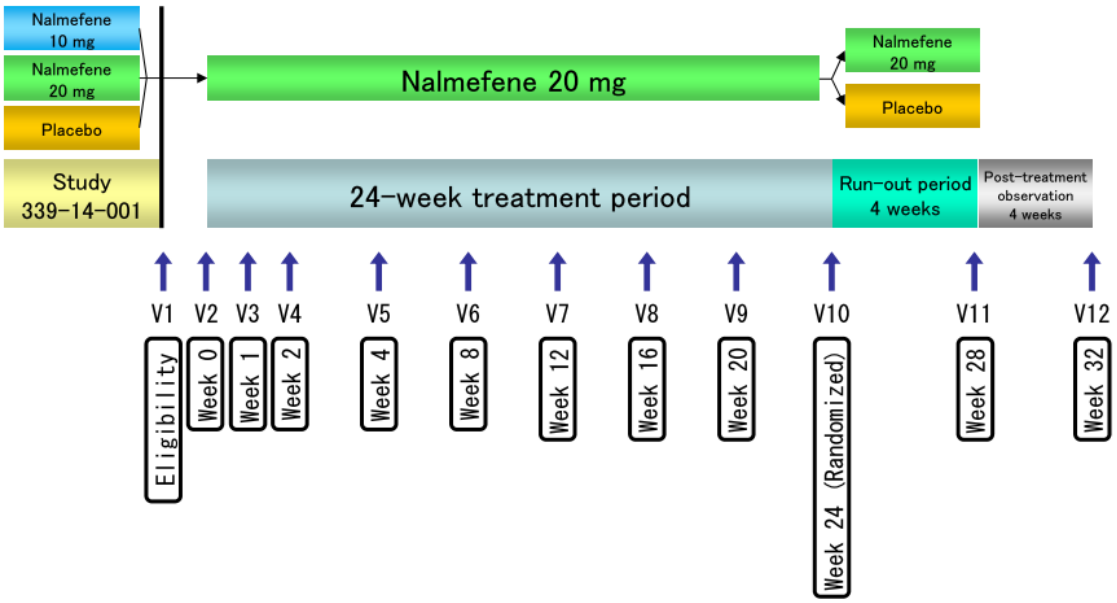

Figure 3.1-1 Summary of Trial Design

V = visit.
Posttreatment observation will be performed only in subjects who complete the run-out period.

3.2 Rationale for Trial Design

3.2.1 Rationale for Dose and Dosage Regimen

This trial is a long-term extension study subsequently conducted following a phase 3 study (Study 339-14-001) to evaluate efficacy and safety of nalmefene hydrochloride at 10 mg and 20 mg in Japanese patients with alcohol dependence. As once-a-day as-needed use at 1 to 2 hours before drinking is employed in the preceding phase 3 study (Study 339-14-001), the same dosage regimen will be used in this extension study. The dose of nalmefene hydrochloride in this extension study is set at 20 mg, the highest dose in the preceding phase 3 study (Study 339-14-001).

3.2.2 Rationale for Trial Duration

Considering the possibility that nalmefene is administered for a long term exceeding 24 weeks in the clinical settings, we have set the treatment duration of this trial at 24 weeks, making the total treatment duration 48 weeks when combined with the 24-week treatment period of the preceding Study 339-14-001. In addition, a 4-week run-

out period has been employed to evaluate any withdrawal symptoms. Based on the above, the duration of the administration in this trial is set at 28 weeks.

3.2.3 Rationale for Run-out Period

In the foreign phase 3 confirmatory trials (Studies 12014A and 12023A), a 4-week run-out period following a 24-week treatment period was adopted in order to evaluate any discontinuation effect of nalmefene hydrochloride. In the present trial, a 4-week run-out period will be adopted with reference to the foreign phase 3 confirmatory trials (Studies 12014A and 12023A), and the discontinuation effects of this drug will be evaluated after the re-randomization to nalmefene hydrochloride group or placebo group. Dependency on this drug will be evaluated with Dependency Assessment Form A.

3.2.4 Rationale for Posttreatment Observation Period

This period is scheduled to evaluate the effects after the long-term treatment with nalmefene hydrochloride. Withdrawal symptoms from this drug will be evaluated with Dependency Assessment Form B.

3.3 Variables

3.3.1 Safety

- Adverse events, clinical laboratory values, blood pressure and pulse rate, body weight, 12-lead ECG, physical examination, POMS, Columbia-Suicide Severity Rating Scale (C-SSRS), and dependence survey

3.3.2 Efficacy

Baseline for the number of HDDs, TAC, and DRL is defined as the data collected by the Timeline Followback (TLFB) method during the period of 4 weeks before the Screening Visit of Study 339-14-001. One month is defined as 4 weeks (28 days) for this trial.

- Change in the number of HDDs from baseline
  (The number of HDDs is defined as the number of days per month [days/month] with alcohol consumption per day of > 60 g for males and > 40 g for females)
- Change in TAC from baseline
  (TAC is defined as mean alcohol consumption per day [g/day] over a 1-month period)

- Response Shift Drinking Risk Level (RSDRL): The percentage of subjects with a downward shift in DRL of 2 categories or more[b] from baseline
- Response Low Drinking Risk Level (RLDRL): The percentage of subjects with a low DRL or below
- 70% TAC responder rate: The percentage of subjects whose TAC is reduced by ≥ 70% from baseline
- HDD responder rate: The percentage of subjects in whom the number of HDDs is ≤ 4
- Clinical Global Impression-Severity of Illness (CGI-S)
- Clinical Global Impression-Global Improvement (CGI-I)
- MOS 36-item Short-form Health Survey (SF-36)
- EuroQol 5 Dimension (EQ-5D)
- Alcohol Quality of Life Scale (AQoLS)
- Resource Use Measurement Questionnaire-Alcohol Dependence (RUMQ-ADP)
- Gamma-glutamyl transferase (GGT)
- Alanine aminotransferase (ALT)

[Rationale for variable selection]

[Safety]

Items necessary for safety evaluation have been selected.

[Efficacy]

The number of HDDs and TAC are set as primary efficacy variables for IMPs aiming at harm reduction in the EMA guideline on the development of medicinal products for the treatment of alcohol dependence,[14] and were used as the co-primary efficacy variables in foreign phase 3 studies of nalmefene hydrochloride. In the present study, the variables were selected with reference to the guideline and the foreign clinical studies.

3.4 Number of Patients Planned

Approximately 400 subjects who advance from Study 399-14-001

[b] A shift to medium DRL or lower for patients with a very high DRL at baseline; a shift to low DRL or below for patients with a high DRL at baseline

4 Investigational Medicinal Products

4.1 Test Product and Comparator

4.1.1 Test Product

Code Name	Lu AA36143
Generic Name	INN: Nalmefene
Chemical Name	17-(cyclopropylmethyl)-4,5α-epoxy-6-methylenemorphinan-3,14-diol
Content and Formulation	White film-coated tablets containing 20 mg (as an anhydride of nalmefene hydrochloride) per tablet
Storage Conditions	Store at room temperature
Supplier	H. Lundbeck A/S

4.1.2 Comparator: Placebo

Content and Formulation	Placebo tablets that are indistinguishable in appearance from nalmefene hydrochloride tablets 20 mg
Storage Conditions	Store at room temperature
Supplier	H. Lundbeck A/S

4.2 Packaging and Labeling

4.2.1 Packaging

Fourteen tablets of nalmefene hydrochloride 20 mg or placebo are packaged in a blister card with a tamper-resistant seal.

4.2.2 Contents of Label

The following information is written on the labels of IMP(s): specification that the drug is for use in a clinical trial, the code name of the IMP, lot number, expiration date, storage conditions, name and address of the sponsor, etc.

5 Trial Population

5.1 Target Disease

Alcohol dependent patients

5.2 Inclusion Criteria

Patients who meet all of the following inclusion criteria will be selected.

1) Patients who have completed Study 339-14-001.
2) Patients who have signed the informed consent form (ICF) for Study 339-14-002.

[Rationale for Inclusion Criteria]

1) This criterion was set to evaluate the safety of long-term treatment with nalmefene hydrochloride.
2) For appropriate assessments of the IMP.

5.3 Exclusion Criteria

Patients who fall under any of the following exclusion criteria at the examination at the end of the treatment period of Study 339-14-001 will be excluded from the trial.

1) The patient has a clinically significant unstable illness (eg, complication of New York Heart Association [NYHA] class III or IV heart failure or angina pectoris, renal function disorder with estimated glomerular filtration rate [eGFR] of < 30 mL/min/1.73 m^2, hepatic failure, and neoplastic disorder).
2) The patient has a clinically significant abnormal ECG which is inappropriate for the participation in the trial in the opinion of the investigator or subinvestigator.
3) The patient satisfies at least one of the following suicide risk criteria:
   - Answers "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) and whose episode meeting criteria for any of these 2 C-SSRS Ideation Items occurred within the last 6 months, OR
   - Answers "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (Actual Attempt [non-fatal], Interrupted Attempt, Aborted Attempt, Preparatory Acts or Behavior, Completed Suicide) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, OR
   - The patient is, in the opinion of the investigator or subinvestigator, at significant risk of suicide.

4) The patient has at least one of the following laboratory findings:
   - Red blood cell count: < 3,000,000/mm^3, hemoglobin: < 9.5 g/dL, white blood cell count: < 3,000/mm^3, platelet count: < 75,000/mm^3
   - Alanine aminotransferase or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN)
5) The patient is mainly engaged in driving or those engaged in potentially hazardous activities, such as operating machinery or working in high place.
6) Women who are pregnant or breast-feeding, who may be pregnant, or who wish to become pregnant during the trial and within 4 weeks after the final IMP administration. Men whose partners wish to become pregnant during the trial and within 4 weeks after the final IMP administration. Also, patients who or whose partners cannot use birth control.
7) Patients otherwise judged by the investigator or subinvestigator to be inappropriate for inclusion in the trial for any reason.

[Rationale for Exclusion Criteria]

1)-5) This criterion was set to ensure subject safety.

6) The safety of nalmefene hydrochloride in fetuses has not been established.

7) For appropriate assessments of the IMP.

Reference: NYHA Classification

Class I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Source: Guidelines for Diagnosis and Treatment of Cardiovascular Diseases (2004-2005 Joint Working Group Report)
[Digest version] Guidelines for Treatment of Acute Heart Failure (2006 revised version)
Academic societies that participated in the joint working groups: The Japanese Circulation Society, The Japanese Association for Thoracic Surgery, The Japanese Society for Cardiovascular Surgery, The Japanese College of Cardiology, and The Japanese Heart Failure Society
http://www.j-circ.or.jp/guideline/pdf/JCS2006_maruyama_d.pdf

Risk Levels Defined by the World Health Organization Based on Average Volume of Alcohol Consumption per Day

DRL	Men	Women
Very high	> 100 g	> 60 g
High	> 60 g - ≤ 100 g	> 40 g - ≤ 60 g
Medium	> 40 g - ≤ 60 g	> 20 g - ≤ 40 g
Low	≥ 1 g - ≤ 40 g	≥ 1 g - ≤ 20 g

6 Trial Design

6.1 Dose, Regimen, and Treatment Period

6.1.1 Dose and Regimen

All subjects will receive a nalmefene hydrochloride tablet 20 mg in the treatment period and either a nalmefene hydrochloride tablet 20 mg or a placebo tablet in the run-out period. Each subject will be instructed to take one tablet (nalmefene hydrochloride 20 mg or placebo) on days when the subject perceives a risk of drinking alcohol, as needed 1 to 2 hours before the anticipated risk of drinking. If the subject has started drinking alcohol without taking the IMP, the subject should take one tablet as soon as possible. The IMP can be taken up to one tablet a day (one day is defined as the period from 0 AM of the day to 0 AM of the next day). Tablets must not be divided.

6.1.2 Treatment Period

28 weeks (24 weeks for a treatment period and 4 weeks for a run-out period)

[Rationale for dose, regimen, and treatment period]

Described in Section 3.2, Rationale for Trial Design.

6.2 Prior and Concomitant Treatment

If a drug other than an IMP has been used during the period from the acquisition of consent to the end of the trial, the name of the drug, purpose of use, mode of administration, daily dose, route of administration, and dates of start and end of administration will be recorded in the case report form (CRF). For a non-drug therapy, the name of therapy, purpose, and dates of start and end of treatment will be recorded in the CRF.

6.2.1 Prohibited Concomitant Drugs and Restricted Concomitant Drugs

Restriction on drugs to be used during the trial is set for each drug class. The prohibited or restricted concomitant drugs (including over-the-counter drugs) in this trial are presented in Table 6.2.1-1. The concomitant use of those drugs will be prohibited or restricted in the period from eligibility confirmation (Visit 1, at the end of the treatment period of Study 339-14-001) until the end of the run-out period (Visit 11) or withdrawal.

Table 6.2.1-1 Prohibited and Restricted Concomitant Therapy

Drug Class	Comments or Exceptions
Agents used for treatment of alcohol dependence	Including oral and injectable naltrexone, acamprosate calcium, topiramate, disulfiram, and cyanamide.
IMPs for other trials and drugs not approved in Japan	-
Opioid analgesics	Non-opioid analgesics are allowed to use.
Opioid antidiarrheal drugs	Non-opioid antidiarrheals are allowed to use.
Antitussive drugs and cold medicines containing opioids	Non-opioid antitussive drugs and cold medicines are allowed to use.
Antidepressants	-
Antipsychotics	-
Anticonvulsants	-
Anxiolytics	As-needed use is allowed.
Hypnotics	As-needed use is allowed.
Anorexics	-
Psychotropic agents not otherwise specified (including herbal agents used against mental disorder)	-
Antineoplastics	-
Muscle relaxants	As-needed use is allowed.
Insulin	-
Anticoagulants	-
Antibiotics with possible interaction with alcohol (nitrofurantoin, metronidazole, and tinidazole)	-
Antifungal agents (systemic)	Local antifungal agents are allowed to use.
Steroids	Local and inhalation steroids, oral contraceptives, and hormone replacement therapy are allowed.

[Rationale for prohibited prior drugs, prohibited concomitant drugs, and restricted concomitant drugs]

Those drugs are prohibited or restricted because they may significantly affect the efficacy and safety of the IMP.

6.2.2 Concomitant Therapies

All subjects will receive BRENDA approach as a psychosocial therapy. It comprises six components covering the most important aspects of a psychosocial therapy for patients with alcohol dependence in a concise manner. In addition, it is a strategy to manage an appropriate treatment for a patient by the collaboration between the treatment provider and the patient. It is used to provide psychosocial support to patients and to ensure and enhance treatment compliance and is particularly well suited in conjunction with pharmacotherapy. In this trial, trained personnel such as the investigator, subinvestigator, and clinical psychologist will perform BRENDA approach at each visit after Week 0 (Visit 2).

At each visit, BRENDA approach will be conducted according to its manual by the investigator, subinvestigator, or other personnel such as clinical psychologist. The investigator or subinvestigator will document the results of BRENDA approach in the medical record and the date of the conduct in the CRF. Psychosocial therapy other than BRENDA approach is not permitted in the period from eligibility confirmation (Visit 1) until the completion of the examination of the run-out period (Visit 11). BRENDA approach comprises the following six components:

- Biopsychosocial evaluation
- Report to the patient on assessment
- Empathic understanding of the patient's situation
- Needs collaboratively identified by the patient and treatment provider
- Direct advice to the patient on how to meet those needs
- Assess reaction of the patient to advice and adjust as necessary for best care

All BRENDA providers are required to be trained and certified to ensure that BRENDA approach is applied according to the manual. Before starting the trial, the sponsor will plan and provide the training for BRENDA approach. Only providers who have received BRENDA training and met the criteria for certification will be authorized to perform BRENDA approach during the trial. Training certificates will be issued to the trained personnel such as the investigator, subinvestigator, and clinical psychologist, and kept by the investigator.

When a new BRENDA provider is added during the trial period, the provider will be certified in accordance with the same procedure.

6.3 Method of Minimizing or Avoiding Bias

An interactive web response system (IWRS) and interactive voice response system (IVRS) will be used in this trial.

The run-out period of this trial is a randomized double-blind phase. The investigator, subinvestigator, and subjects are blind to the IMP randomization code. The sponsor's trial staff, including personnel of contract research organizations, are also unable to access the IMP randomization code during the trial period.

The randomization table will be kept under strict control by the IMP allocation manager until unblinding after fixation of all CRFs and the database.

The emergency code list will be controlled by the IWRS and IVRS until the end of the trial, and, if a medical emergency occurs in a subject and knowledge of his or her IMP randomization code is considered important for treatment, the emergency code will be broken according to Section 8.2.3, Emergency Code Breaking (Procedure for Unblinding During the Trial Period).

When IMPs are recovered by the sponsor prior to unblinding, they are to be recovered sealed by the study drug manager.

7 Trial Procedures

7.1 Schedule and Procedures

The schedule of observations, examinations, and evaluations is shown in Table 7.1-1. The investigator or subinvestigator will perform observations, examinations, and evaluations in accordance with this schedule. Items that trial associates are capable of performing, such as the subject demographic survey and clinical laboratory tests, may be performed by trial associates under the supervision of the investigator.

Table 7.1-1 Trial Schedule

		Treatment Period									Run-out Period	Post-treatment Observation	Withdrawal[b]
Visit	**V1[a] (Eligibility)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10 (Randomized)**	**V11**	**V12**	
Week		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	
Day		**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	
Acceptable time window for visit (Day)[c]	**−7**	**0**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	
Signed informed consent[d]	●												
Demographics	■												
BAC[e]		●	●	●	●	●	●	●	●	●	●	●	●
Inclusion/exclusion criteria	●												
Randomization										●			
Efficacy Assessments													
TLFB[f,g]		●	●	●	●	●	●	●	●	●	●		●
CGI-S[g]		●	●	●	●	●	●	●	●	●	●		●
CGI-I		●	●	●	●	●	●	●	●	●	●		●
SF-36[g]							●			●	●		●
EQ-5D[g]							●			●	●		●
AQoLS[g]							●			●	●		●
RUMQ-ADP[g]							●			●	●		●
GGT[g]	■						●			●	●		●
ALT[g]	■						●			●	●		●
Safety Assessments													
AEs	◄												►
Clinical laboratory tests[g]	■						●			●	●	●	●
Vital signs and body weight[g]		●	●	●	●	●	●	●	●	●	●	●	●
12-lead ECG[g]	■						●			●	●	●	●
Examinations (physical)[g]							●			●	●	●	●
POMS[g]							●			●	●	●	●
C-SSRS[g]	■	●	●	●	●	●	●	●	●	●	●	●	●
Assessment of dependency A											●		
Assessment of dependency B												●	
Others													
BRENDA approach		●	●	●	●	●	●	●	●	●	●	●	●
IMP dispensed		●	●	●	●	●	●	●	●	●			
IMP returned and IMP accountability			●	●	●	●	●	●	●	●	●		●
Concomitant drugs and therapies	◄												►
Assessment of the newly started treatment for alcohol dependence												●	●
Pregnancy test[h]	■	●	●	●	●	●	●	●	●	●	●	●	●

BAC = breath alcohol concentration; V = visit

■ The data at the visit at the end of the treatment period (Visit 10) of Study 339-14-001 will be used.

[a]Visit 1 of Study 339-14-002 and the visit at the end of the treatment period (Visit 10) of Study 339-14-001 will be performed at the same time.

[b]This visit should take place as soon as possible after the withdrawal is decided. If a subject drops out before the start of the treatment period, the withdrawal examination will not be conducted, but the follow-up will be performed at 4 weeks after the completion of the treatment period of Study 339-14-001. If a subject is withdrawn after the completion of the run-out period, efficacy evaluation (TLFB, CGI-S, CGI-I, SF-36, EQ-5D, AQoLS, and RUMQ-ADP) will be unnecessary.

[c]If a date of a subject visit does not conform to the acceptable time window for the visit, subsequent visits should be planned to maintain the visit schedule relative to Week 0 (the start date of the treatment period, Visit 2).

[d]Informed consent for this trial will be obtained before the completion of Study 339-14-001.

[e]A breath alcohol concentration (BAC) will be obtained at each visit with a breath analyzer. A BAC will be the first procedure at the visits. If the BAC is ≥ 0.1 mg/L, the subject should visit the site again at a later date within the acceptable time window to undergo observations, examinations, and evaluations.

[f]With TLFB, alcohol consumption data in the period between the current visit and last visit will be collected at each visit. Subjects may use supplementary materials for TLFB such as their personal calendars or a calendar provided by the site to help in recalling their drinking behaviors. Supplementary materials will be used as a memory aid to support subjects' input to TLFB but not as source documents. NB: The TLFB may only be completed by a trained and certified rater.

[g]The data at the Screening Visit (Visit 1) of Study 339-14-001 will be used as baseline data for these endpoints.

[h]Pregnancy test will be performed only in female subjects of childbearing potential. It is not necessary to perform pregnancy test in subjects without childbearing potential due to surgery such as hysterectomy and bilateral oophorectomy or subjects who have had menopause for at least 12 months.

7.1.1 Acquisition of Informed Consent

The investigator or subinvestigator will obtain written consent directly from subjects before the completion of Study 339-14-001. The date of informed consent acquisition will be recorded in the CRF.

7.1.2 Subject Registration

A subject number (3-digit trial site number + S + 5-digit in-site serial number) for each subject will be used continuously in Study 339-14-001 and this trial. After obtaining informed consent from a subject, the investigator, subinvestigator, or trial associate will access the IWRS or IVRS to receive a subject number for the subject who has signed the written information/ICF.

7.1.3 Eligibility Confirmation (Examinations at the End of the Treatment Period of Study 339-14-001)

1) For eligibility confirmation for this trial, the results of the following examinations at the end of the treatment period of Study 339-14-001 will be used. Eligibility will be confirmed within 1 week after the examinations at the end of the treatment period of Study 339-14-001.

- Clinical laboratory tests
- 12-lead ECG
- C-SSRS
- Pregnancy test (only in female subjects of childbearing potential)

2) From the results of the examinations at the end of the treatment period of Study 339-14-001, the investigator or subinvestigator will verify that each subject meets the inclusion criteria and does not fall under any of the exclusion criteria and will start the treatment period after registering the subject according to Section 7.1.2, Subject Registration. The data on the efficacy endpoints of Study 339-14-001 will be recorded in the CRF before the start of the treatment period (Visit 2).

7.1.4 Observations, Examinations, and Evaluations During the Treatment Period

7.1.4.1 Week 0 (Start Date of the Treatment Period, Visit 2), Week 1 (Visit 3), Week 2 (Visit 4), Week 4 (Visit 5), Week 8 (Visit 6), Week 12 (Visit 7), Week 16 (Visit 8), and Week 20 (Visit 9)

According to the procedures shown in Section 7.2, Method of Evaluation, the following will be performed within the acceptable time window of ± 3 days until Week 2 (Visit 4) and within the acceptable time window of ± 7 days at Week 4 (Visit 5) to Week 20 (Visit 9).

- Measurement of BAC* (it will be the first procedure at each visit)
- TLFB (alcohol consumption data after last visit will be collected)
- CGI-S
- CGI-I
- SF-36 (Week 12 [Visit 7])
- EQ-5D (Week 12 [Visit 7])
- AQoLS (Week 12 [Visit 7])
- RUMQ-ADP (Week 12 [Visit 7])
- AEs
- Clinical laboratory tests (Week 12 [Visit 7])
- Blood pressure and pulse rate, and body weight
- 12-lead ECG (Week 12 [Visit 7])
- Physical examination (Week 12 [Visit 7])
- POMS (Week 12 [Visit 7])
- C-SSRS
- Concomitant drugs and therapies

- Pregnancy test (only in female subjects of childbearing potential)
- Evaluation of treatment compliance (except for Week 0 [Visit 2])

*: If the BAC is ≥ 0.1 mg/L, the subject should visit the site again at a later date within the acceptable time window to undergo observations, examinations, and evaluations.

7.1.4.2 Week 24 (End of the Treatment Period, Visit 10)

1) According to the procedures shown in Section 7.2, Method of Evaluation, the following will be performed within the acceptable time window of ± 7 days.

- Measurement of BAC* (it will be the first procedure at the visit)
- TLFB (alcohol consumption data after last visit will be collected)
- CGI-S
- CGI-I
- SF-36
- EQ-5D
- AQoLS
- RUMQ-ADP
- AEs
- Clinical laboratory tests
- Blood pressure and pulse rate, and body weight
- 12-lead ECG
- Physical examination
- POMS
- C-SSRS
- Concomitant drugs and therapies
- Pregnancy test (only in female subjects of childbearing potential)
- Evaluation of treatment compliance

*: If the BAC is ≥ 0.1 mg/L, the subject should visit the site again at a later date within the acceptable time window to undergo observations, examinations, and evaluations.

2) Randomization (allocation of IMPs to subjects)
The investigator or subinvestigator will enter information on subjects who have completed the treatment period in the IWRS or IVRS for randomization. The IWRS or IVRS will randomize each subject to one of the treatment groups and allocate an IMP number to the subject.

7.1.5 Week 28 (Run-out Period, Visit 11)

According to the procedures shown in Section 7.2, Method of Evaluation, the following will be performed within the acceptable time window of ± 7 days.

- Measurement of BAC* (it will be the first procedure at the visit)
- TLFB (alcohol consumption data after last visit will be collected)
- CGI-S
- CGI-I
- SF-36
- EQ-5D
- AQoLS
- RUMQ-ADP
- AEs
- Clinical laboratory tests
- Blood pressure and pulse rate, and body weight
- 12-lead ECG
- Physical examination
- POMS
- C-SSRS
- Assessment of dependency A
- Concomitant drugs and therapies
- Pregnancy test (only in female subjects of childbearing potential)
- Evaluation of treatment compliance

*: If the BAC is ≥ 0.1 mg/L, the subject should visit the site again at a later date within the acceptable time window to undergo observations, examinations, and evaluations.

7.1.6 Week 32 (Posttreatment Observation, Visit 12)

Only in subjects who have completed the run-out period, the following will be performed within the acceptable time window of ± 7 days at 4 weeks after the end of the run-out period according to the procedures shown in Section 7.2, Method of Evaluation.

- Measurement of BAC* (it will be the first procedure at the visit)
- AEs
- Clinical laboratory tests
- Blood pressure and pulse rate, and body weight
- 12-lead ECG

- Physical examination
- POMS
- C-SSRS
- Assessment of dependency B
- Concomitant drugs and therapies
- Assessment of the newly started treatment for alcohol dependence
- Pregnancy test (only in female subjects of childbearing potential)

*: If the BAC is ≥ 0.1 mg/L, the subject should visit the site again at a later date within the acceptable time window to undergo observations, examinations, and evaluations.

7.1.7 Time of Withdrawal

Examinations, observations, and evaluations will be performed as soon as possible after the withdrawn is decided. If a subject drops out before the start of the treatment period, the withdrawal examination will not be conducted, but the follow-up will be performed at 4 weeks after the completion of the treatment period of Study 339-14-001. If a subject is withdrawn after the completion of the run-out period, efficacy evaluation (TLFB, CGI-S, CGI-I, SF-36, EQ-5D, AQoLS, and RUMQ-ADP) will be unnecessary. If the subject refuses to undergo any examinations at the time of withdrawal, or if the investigator or subinvestigator judges that any examinations cannot be performed due to an emergency or other circumstances, of the examination items specified for the time of withdrawal, only those items that can be performed will be performed.

- Measurement of BAC* (it will be the first procedure at the visit)
- TLFB (alcohol consumption data after last visit will be collected)
- CGI-S
- CGI-I
- SF-36
- EQ-5D
- AQoLS
- RUMQ-ADP
- AEs
- Clinical laboratory tests
- Blood pressure and pulse rate, and body weight
- 12-lead ECG
- Physical examination

- POMS
- C-SSRS
- Concomitant drugs and therapies
- Assessment of the newly started treatment for alcohol dependence
- Pregnancy test (only in female subjects of childbearing potential)
- Evaluation of treatment compliance

*: If the BAC is ≥ 0.1 mg/L, the subject should visit the site again at a later date within the acceptable time window to undergo observations, examinations, and evaluations.

7.1.8 Follow-up Investigation

If an AE has not resolved on the day of posttreatment observation examination or on the day of withdrawal, the AE will be followed up in accordance with Section 8.4, Follow-up Investigation of Adverse Events.

7.2 Method of Evaluation

7.2.1 Safety

7.2.1.1 Clinical Laboratory Values

Blood samples for hematology and blood chemistry and urine samples for urinalysis listed in Table 7.2.1.1-1 will be taken. These samples will be analyzed at the central clinical laboratory. The laboratory test results at the end of the treatment period of Study 339-14-001 will be used for eligibility confirmation for this trial (Visit 1).

The sponsor will collect test results from the central clinical laboratory. The investigator or subinvestigator will record the dates of blood and urine collection in the CRF. The procedures for sampling, processing, storage, shipping, and measurement will be in accordance with the standard operating procedures.

Table 7.2.1.1-1 Clinical Laboratory Tests

Hematology Red blood cell count Hematocrit Hemoglobin MCV Total white blood cell count Neutrophils (% of total leucocytes) Eosinophils (% of total leucocytes) Basophils (% of total leucocytes) Lymphocytes (% of total leucocytes) Monocytes (% of total leucocytes) Platelet count	**Liver** Total bilirubin Alkaline phosphatase ALT[a,b] AST[b] GGT[a] P-INR/prothrombin time Albumin Cholinesterase	**Kidney** Creatinine BUN	**Infection** CRP
		Electrolytes Sodium Potassium Bicarbonate (HCO_3^-) Calcium	**Urine** Protein Glucose Occult blood Ketones HCG[c] Urinary sediment
	Lipids Total cholesterol Triglycerides	Nutritional Albumin Glucose	Others Prolactin

BUN = blood urea nitrogen; CRP = C-reactive protein; HCG =human chorionic gonadotropin; INR = international normalized ratio; MCV = mean corpuscular volume.

[a]These tests will be used for secondary efficacy analysis as well as safety analysis.

[b]If ALT or AST is > 5 times the ULN, it should be monitored more frequently.

[c]This test will be performed only in female subjects of childbearing potential.

7.2.1.2 Blood Pressure and Pulse Rate, and Body Weight

Systolic and diastolic blood pressures will be measured in a sitting position after a 5-minute rest. Pulse rate will be recorded after blood pressure measurement.

Subjects will be weighed while wearing light clothing and no shoes.

The investigator or subinvestigator will record the dates and results of the measurement of blood pressure, pulse rate, and body weight in the CRF. Those measurements will be performed before collecting blood in principle when blood sampling is scheduled.

7.2.1.3 Twelve-lead Electrocardiogram

The results of 12-lead ECG at the end of the treatment period of Study 339-14-001 will be used for eligibility confirmation for this trial (Visit 1).

A 12-lead ECG will be recorded with an ECG equipment provided by the sponsor. The ECG will be transferred electronically to the central ECG laboratory. The sponsor will collect the results of evaluation (heart rate, RR interval, PR interval, QRS interval, QT interval, QT interval as corrected by Bazett's formula [QTcB], QT interval as corrected by Fridericia's formula [QTcF], and assessment based on the ECG abnormality criteria) from the central ECG laboratory.

The investigator or subinvestigator will record the dates of ECG recording in the CRF.

7.2.1.4 Physical Examination

In physical examination, the investigator or subinvestigator will examine the appearance, extremities, skin, head, neck, eyes, ears, nose, throat, lungs, chest, heart, abdomen, genitourinary system, and musculoskeletal system at a minimum. The investigator or subinvestigator will record the dates and results of physical examination in the CRF.

7.2.1.5 Profile of Mood States

Profile of Mood States has been developed to assess transient distinct mood states. This scale is a self-report inventory. The scale measures the following 6 factors: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. It allows calculation of a total mood disturbance (TMD) score. Each item is rated on a 5-point scale ranging from 0 (not at all) to 4 (extremely) based on how well each item describes a subject's mood in the past week.

Subjects will complete POMS for themselves. The investigator or subinvestigator will record the dates and results of POMS assessment in the CRF.

7.2.1.6 Columbia-Suicide Severity Rating Scale

The results of C-SSRS at the end of the treatment period of Study 339-14-001 will be used for eligibility confirmation for this trial (Visit 1).

The investigator or subinvestigator will perform post-baseline assessment to focus on suicidality after last trial visit (suicidality after the end of the treatment period of Study 339-14-001 for Week 0 [start of the treatment period, Visit 2]). The investigator or subinvestigator will record the dates and results of these assessments in the CRF.

7.2.1.7 Dependency Assessment

Dependency assessment is an index to assess dependency on nalmefene hydrochloride. Dependency Assessment Form A and Form B comprise 10 items and 6 items, respectively, and each item will be rated on a 4-point scale ranging from 1 (very much) to 4 (no).

The investigator or subinvestigator will perform the dependency assessment and record the dates and results of assessment in the CRF.

7.2.2 Efficacy Evaluation

7.2.2.1 Timeline Followback

Timeline Followback is a method to estimate alcohol consumption per day. Subjects will be instructed to recall their drinking behaviors retrospectively and provide their estimated alcohol consumption per day using a standard unit of drinks. One day is defined as a 24-hour period starting at 6 AM and ending at 6 AM of the next morning. Alcohol consumption data between last visit and the current visit will be collected at each visit. If a visit is missed, the data that should have been provided at the missed visit will be collected at the next visit. Subjects may use supplementary materials for TLFB such as their personal calendars or a calendar provided by the site to help in recalling their drinking behaviors. Supplementary materials will be used as a memory aid to support subjects' input to TLFB but not as source documents. The dates of TLFB and alcohol consumption data collected at visits will be recorded in the CRF.

Timeline Followback will be administered by site personnel such as the investigator, subinvestigator, and clinical psychologist according to the manual at each visit. To be certified as a TLFB rater before the trial, it is not necessary to have previous experience with TLFB. Before starting the trial, the sponsor will plan and provide the training for TLFB. Only raters who have received TLFB training and met the criteria for certification will be authorized to perform TLFB during the trial. Training certificates will be issued to the certified personnel such as the investigator, subinvestigator, and clinical psychologist, and kept by the investigator.

When a new rater is added during the trial, the rater will be certified in accordance with the same procedure.

Each subject must be assessed by the same rater throughout the trial period wherever possible.

7.2.2.2 Clinical Global Impression-Severity of Illness and Clinical Global Impression-Global Improvement

The Clinical Global Impression (CGI) scale comprises 2 subscales of CGI-S and CGI-I.

The CGI-S scale is used by clinicians when assessing their global impression of a patient's current clinical condition. The investigator or subinvestigator will use his/her clinical experience with this patient population to rate the severity of a subject's clinical condition on a 7-point scale.

The CGI-I scale is used to assess a patient's improvement (or worsening). The investigator or subinvestigator is required to assess a subject's condition relative to baseline at the Screening Visit of Study 339-14-001 on a 7-point scale. In all cases, the rater should assess a subject's condition independent of whether the subject's improvement is related to the IMP or not.

The investigator or subinvestigator will record the dates and results of CGI-S and CGI-I assessments in the CRF.

Only trained raters will administer CGI-S and CGI-I. To be certified, the investigator or subinvestigator will be required to receive training. When a new rater is added during the trial, the rater will be certified in accordance with the same procedure.

The CGI scale will be used to assess the mental condition of alcohol dependence. Mental conditions other than alcohol dependence should not be considered in the CGI assessment.

7.2.2.3 MOS 36-item Short-form Health Survey

MOS 36-item Short-form Health Survey has been developed as a general measure of subjective health condition perceived by patients. It is a self-rating questionnaire comprising 36 questions, and can measure 8 health concepts: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, mental health, emotional role functioning, and social role functioning. It can also measure 2 summary scores as the comprehensive scales for the quality of life related to health: Physical Component Summary which is focused on physical conditions and Mental Component Summary which is focused on mental conditions. The SF-36 has been demonstrated to be useful in monitoring general and specific populations, comparing the burdens of different diseases, differentiating the health benefits by treatment, and screening individual patients.

Subjects will complete SF-36 for themselves. The investigator or subinvestigator will record the dates and results of SF-36 assessment in the CRF.

7.2.2.4 EuroQol 5 Dimension

EuroQol 5 Dimension is a measure of health outcome. It comprises 5 items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analog scale (VAS). The 5 items allow the calculation of a utility index ranging between 0 (the worst) and 1 (the best). The VAS ranges between 0 (the worst imaginable health state) and 100 (the best imaginable health state).

Subjects will complete EQ-5D for themselves. The investigator or subinvestigator will record the dates and results of EQ-5D assessment in the CRF.

7.2.2.5 Alcohol Quality of Life Scale

Alcohol Quality of Life Scale is an index to assess the consequences of alcohol drinking in a patient over the past 4 weeks, and is a self-rating questionnaire comprising 34 questions.

Subjects will complete AQoLS for themselves. The investigator or subinvestigator will record the dates and results of AQoLS assessment in the CRF.

7.2.2.6 Resource Use Measurement Questionnaire-Alcohol Dependence

Resource Use Measurement Questionnaire-Alcohol Dependence has been developed to collect information on resources used by a patient with alcohol dependence during the last 3 months. Information collected includes the following:

- Health care related to the management of alcohol intoxication including hospitalization, consultations, and home-visit nursing
- Health care related to the management of comorbidities including hospitalization, consultations, physiotherapy/kinesitherapy, and home-visit nursing
- Sick leaves: frequency and duration

The investigator or subinvestigator will administer RUMQ-ADP and record the dates and results of assessment in the CRF.

7.2.3 Others

7.2.3.1 Breath Alcohol Concentration

At each visit, BAC will be measured with a breath analyzer. The BAC measurement will be the first procedure at each visit, and the observations, examinations, and evaluations specified in the trial will be performed only when the BAC is < 0.1 mg/L. If the BAC is ≥ 0.1 mg/L, the subject should visit the site again at a later date within the acceptable time window to undergo the observations, examinations, and evaluations. The dates and results of the BAC measurement will be recorded in the CRF.

7.2.3.2 Pregnancy Test

Pregnancy test will be performed only in female subjects of childbearing potential. It is not necessary to perform pregnancy test in subjects without childbearing potential due to surgery such as hysterectomy and bilateral oophorectomy or subjects who have had

menopause for at least 12 months. Serum pregnancy test will be performed only if pregnancy is suspected according to the result of urine pregnancy test. The dates and results of pregnancy test will be recorded in the CRF.

7.2.4 Investigational Medicinal Product Compliance

Based on the report from each subject, the dates of IMP administration, the number of taken tablets, and the timing of IMP administration (before/after drinking) will be recorded in the CRF. Subjects may make a note of the dates of IMP administration in the margin of the IMP blister card as a memory aid. For IMP compliance, the reports from subjects at visits will be regarded as source documents. The notes used as a memory aid will not be source documents.

7.3 Measures to Be Taken for Subjects Visiting or Planning to Visit Other Hospitals or Departments

At the time of obtaining informed consent, the investigator or subinvestigator will confirm whether or not the subject is receiving treatment at another hospital or department. If the subject is receiving treatment at another hospital or department, the investigator or subinvestigator will inform the attending physician of that hospital or department about the subject's participation in the clinical trial and the IMP being used, with the subject's consent. The investigator or subinvestigator will also obtain and record in the CRF information on the treatment that the subject is receiving at the other hospital or department (name of disease being treated and information on the type of treatment or measures being implemented) and judge whether or not the subject should participate in the trial.

If a subject visits another hospital or department during the trial period, the investigator or subinvestigator will inform the attending physician of that hospital or department about the subject's participation in the clinical trial and the IMP being used, with the subject's consent. The investigator or subinvestigator will also obtain and record in the CRF information on the treatment that the subject receives at the other hospital or department (name of disease treated and information on the type of treatment or measures implemented) and judge whether or not the subject should continue to participate in the trial.

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Event

[International Conference on Harmonisation (ICH) E2A guideline: Definition]

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
>
> An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[c]

For this trial, the term "medical product" is regarded as "IMP," and to secure the safety of subjects, AEs occurring from consent and from the end of the treatment period in Study 339-14-001 (Visit 10) to the start of IMP administration are included in the definition of AEs in addition to the definition given by ICH.

If an event, symptom, or sign existing at the time of acquisition of informed consent in the trial and at the end of the treatment period in Study 339-14-001 (Visit 10) worsens, the exacerbation will be treated as a new AE.

8.1.2 Serious Adverse Event

A serious AE is defined as an AE corresponding to one of the events listed in 1) to 6) below.[c]

The seriousness of AEs occurring during the period from consent and from the end of the treatment period in Study 339-14-001 (Visit 10) to the start of IMP administration will also be judged.

1) An event resulting in death
2) A life-threatening event

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[c]"Clinical Safety Data Management," Notification No. 227 of the Examination Division, Pharmaceutical Affairs Bureau dated 20 Mar 1995 (ICH E2A).

The term "life-threatening" refers to an event in which the patient was at a risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, had it been more severe.

3) An event requiring in-patient hospitalization or prolongation of existing hospitalization for treatment
4) An event resulting in persistent or significant disability/incapacity
5) An event causing a congenital anomaly/birth defect
6) A major event resulting in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in 1) to 5) above. Examples of such events are intensive treatment in an emergency room for bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Explanation of hospitalization for treatment of a serious AE:

Hospitalization for treatment means that the subject must be hospitalized at a medical institution for treatment of an AE, typically for at least one night. This includes hospitalization for treatment of the AE in which no particular medical procedures are carried out (rest therapy). However, it does not include hospitalization for undergoing tests or treatment for an underlying disease or complication that has not worsened since the subject's entry into the trial, hospitalization for social reasons or convenience not intended for treatment of the AE, or hospitalization for treatment or tests scheduled prior to participation in the trial.

8.2 Response to Occurrence of Adverse Events

8.2.1 Actions to Be Taken for Subjects

The investigator or subinvestigator will provide adequate medical care for all clinically significant, trial-related AEs throughout the period of subject participation in the trial as well as thereafter. If treatment for an AE is necessary, the subject will be informed of this.

8.2.2 Expedited Reporting of Serious Adverse Events

(1) Serious AEs Requiring Expedited Reporting

1) Any serious AEs occurring during the trial period regardless of causal relationship with the IMP
2) Serious AEs occurring during the follow-up period (see 8.4, Follow-up Investigation of Adverse Events), if a follow-up investigation is performed, for which a causal relationship with the IMP cannot be ruled out, or AEs that become

serious during the follow-up period for which a causal relationship with the IMP cannot be ruled out

3) Among serious AEs occurring after completion of the trial (after the follow-up investigation, if a follow-up investigation is performed) and reported by subjects to the investigator or subinvestigator, those for which the investigator or subinvestigator cannot rule out a causal relationship with the IMP

(2) Procedures for Expedited Reporting

1) When an AE falling under any of the above items 1) to 3) occurs, the investigator or subinvestigator will notify the sponsor promptly after becoming aware of the event (within 24 hours, in principle) orally or by telephone or e-mail (refer to Annex 1, Emergency Contact).
2) The investigator will then promptly submit a detailed report on any serious AEs occurring after the start of IMP administration to the head of the trial site and the sponsor within 10 days after becoming aware of them using the report form of the trial site or sponsor. Any additional information will also be promptly relayed to the sponsor (within 24 hours, in principle) orally or by telephone or e-mail, and additional reporting will be performed if necessary.
3) When the investigator or subinvestigator is requested by the sponsor, the head of the trial site, or the institutional review board (IRB) to prepare additional information (autopsy report, terminal care report, or other required information) on a reported serious AE, the investigator or subinvestigator will respond to the request.

8.2.3 Emergency Code Breaking (Procedure for Unblinding During the Trial Period)

In the event of a medical emergency such as the occurrence of a serious AE, if the investigator or subinvestigator judges that emergency code breaking is necessary to ensure the safety of the subject, he or she can obtain the emergency code of the subject from the IWRS or IVRS in accordance with the specified procedures (see the corresponding parts of the IWRS and IVRS manual provided separately). Upon breaking of the emergency code, the investigator or subinvestigator will promptly inform the sponsor of it, make a record of the reason for code breaking and the process, and submit it to the sponsor. The IMP cannot be administered again to the subject whose emergency code has been broken.

8.3 Assessment of Adverse Events

The investigator or subinvestigator will assess AEs for the following items.

8.3.1 Terms for Adverse Events

If the disease responsible for an AE can be specified, the name of the diagnosed disease will be recorded in the CRF and not the individual symptoms.

8.3.2 Date of Onset and Recovery

- Date of onset:
  The date of onset of an AE or date of confirmation of an AE will be recorded in the CRF. If an event, symptom, or sign existing at the time of acquisition of informed consent worsens, the date of exacerbation will be recorded in the CRF as "date of onset of AE." Also, if an AE occurring between the acquisition of informed consent and start of IMP administration worsens after administration of the IMP, the exacerbation will be recorded in the CRF as a new AE with the date of exacerbation recorded as "date of onset of exacerbated AE."
- Date of recovery:
  The date of recovery of an AE or date of confirmation of recovery of an AE will be recorded in the CRF.

8.3.3 Severity

Severity of AEs will be classified using the following three categories.

1) Mild
   Discomfort noticed, but no disruption to daily activity
2) Moderate
   Discomfort sufficient to limit or affect normal daily activity
3) Severe
   Inability to work or perform normal daily activity

8.3.4 Causal Relationship With Investigational Medicinal Product

The causal relationship between the IMP and AEs occurring after the start of IMP administration will be judged according to the following two categories.

1) Relationship is ruled out
   For reasons such as the following, the possibility of a relationship between occurrence of an AE and the IMP is not reasonably conceivable.
   a) The event can be assumed to be caused by an underlying disease, complication(s), or previous disease(s).
   b) The event can be assumed to be associated with age, sex, or some other demographic factor.
   c) A temporal relationship between IMP administration and occurrence of the AE is unlikely.

Example: An AE that occurs after a considerable lapse of time from the conclusion of IMP administration.

d) Considering the time course of the AE and IMP administration, a relationship with the IMP is unlikely.
Example: Despite continuous administration of the IMP, the AE disappeared spontaneously without any treatment (except cases in which it is judged that the subject became habituated to the IMP during continued administration).

e) The event can be assumed to be caused by concomitant drug(s).

f) The event can be assumed to be incidental (such as an accident or incidental disease).
Example: "femoral bone fracture" occurring in a traffic accident.

g) A relationship with the IMP can be ruled out for other reasons based on medical consideration.

2) Relationship cannot be ruled out

For reasons such as the following, the possibility of a relationship between occurrence of an AE and the IMP is reasonably conceivable.

a) A relationship is predictable from the pharmacological and toxicological effects of the IMP.
Examples: Occurrence of "pancytopenia" when effects on the hematopoietic system have been observed in nonclinical studies, or the occurrence of "dehydration" when the drug has a diuretic effect.

b) The event has been observed in previous nonclinical studies and/or clinical studies.

c) A temporal relationship is suspected between IMP administration and onset of the AE.
Example: "Allergic dermatitis" occurring several days after the start of IMP administration.

d) A relationship is suspected based on the outcome of an AE after discontinuation or dose reduction of the IMP.
Example: Prompt disappearance of "nausea" after discontinuation of the IMP.

e) A relationship with the IMP cannot be ruled out for other reasons based on medical consideration.

8.3.5 Actions to Be Taken Regarding IMP Administration

Actions to be taken regarding IMP administration following the occurrence of an AE after initiation of IMP administration will be selected from among the following.

- No change
- Discontinuation of IMP administration
- Unknown

- Not applicable
  Example: Cases where the subject died or the AE occurred after the end of the treatment period.

8.3.6 Actions to Be Taken for Adverse Events

The performance of medical treatments (medications and/or other treatments) for AEs and details of the treatments will be described in the CRF.

8.3.7 Outcome

The outcome of an AE will be selected from the following six categories (one only).

If the subject died, the date of death will be recorded in the CRF; if the subject's condition was recovering/resolving, not recovered/not resolved, or unknown, the date of outcome confirmation will be recorded in the CRF.

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown (for some reason, a follow-up investigation could not be performed even once)

8.4 Follow-up Investigation of Adverse Events

The term "recovered" used below means that a subject who had an AE prior to the start of IMP administration returned to his or her original condition, or a subject who had an AE after the start of IMP administration returned to his or her condition before the start of IMP administration.

1) If an AE has not resolved by the day of the posttreatment observation examination (final observation day) or the day of withdrawal, the investigator or subinvestigator will explain to the subject the need for follow-up investigation after the completion of the posttreatment observation or withdrawal and request the subject's cooperation. The investigator or subinvestigator will conduct a follow-up investigation within 4 weeks after the end of the trial and record information regarding the AE in the subject's medical records. If an AE has not resolved by the day of the posttreatment observation examination (final observation day) or the day of withdrawal, the investigator or subinvestigator will record the outcome in the CRF as "recovering/resolving", "not recovered/not resolved", or as otherwise appropriate.

2) If an AE has not resolved by the day of the follow-up investigation and a causal relationship with the IMP cannot be ruled out, follow-up investigation will be continued until the event resolves or becomes stable and information regarding the AE will be recorded in the subject's medical records. If a causal relationship between the AE and the IMP can be ruled out, no further follow-up will be made beyond the day of the initial follow-up investigation.
3) If, between the day of the posttreatment observation examination (final observation day) or the day of withdrawal and the day of the follow-up investigation, a new serious AE for which a causal relationship with the IMP cannot be ruled out occurs, or if an AE that has not resolved by the day of the posttreatment observation examination (final observation day) or the day of withdrawal and for which a causal relationship with the IMP cannot be ruled out becomes serious, follow-up investigation will be conducted until the AE resolves or becomes stable and information regarding the AE will be recorded in the subject's medical records.
4) If a serious AE for which a relationship with the IMP cannot be ruled out is discovered after the day of the posttreatment observation examination (final observation day) or the day of withdrawal, or after the day of the initial follow-up investigation (if performed), follow-up investigation will be conducted until the AE resolves or becomes stable or until follow-up of the subject becomes impossible and information regarding the AE will be recorded in the subject's medical records.

8.5 Pregnancy

If women of childbearing potential or male subjects whose partners are capable of becoming pregnant participate in the trial, the investigator or subinvestigator will attend to the following.

- Information on reproductive and developmental toxicity of the IMP
- Information regarding pregnancy in the ICF
- Explanation of contraceptive methods
- Reporting and follow-up of cases of pregnancy

8.5.1 Guidance to Subjects Including Contraceptive Methods

1) Before the start of the trial, the investigator or subinvestigator will explain to the subjects the importance of using contraception and the risks associated with pregnancy of a female subject or partner of a male subject and, after subjects have read the written information for subjects and understood it, the investigator or subinvestigator will have subjects sign the ICF.
2) If women of childbearing potential or male subjects whose partners are capable of becoming pregnant wish to participate in the trial, the investigator or

subinvestigator will instruct them to practice contraception during the period specified in the trial protocol.

3) Contraceptive methods include condoms, pills, pessaries, intrauterine device, vasectomy, and tubal ligation. However, if a female subject or male subject's partner is without question unable to become pregnant (ie, has undergone bilateral ovariectomy or hysterectomy or has not experienced menses for at least 12 consecutive months for whatever other medical reasons, or the male subject/partner has undergone bilateral orchidectomy), or if the subject and his/her partner remain abstinent, use of contraception is unnecessary.
4) The investigator or subinvestigator will instruct the subjects that if the contraceptive measures fail and evidence of pregnancy of the female subject or male subject's partner such as delay in menstruation is observed, this should be promptly reported to the investigator or subinvestigator.

8.5.2 Actions to Be Taken by the Investigator or Subinvestigator When Pregnancy Is Suspected

If the investigator or subinvestigator or a subject suspects that the subject has become pregnant before initiation of IMP administration, initiation of IMP administration will be withheld and a pregnancy test will be performed. If the test result is positive, the trial subject will be withdrawn without receiving IMP administration. If a pregnancy is suspected after initiation of IMP administration, IMP administration will be discontinued (refer to Section 9.2, Criteria and Procedures for Withdrawal of Individual Subjects).

8.5.3 Actions to Be Taken by the Investigator or Subinvestigator When a Subject Is Discovered to Be Pregnant

When a female subject is found to be pregnant, the investigator or subinvestigator will withdraw the subject from the trial and perform follow-up investigation until delivery or end of pregnancy, and report this in writing to the sponsor.

After discontinuation of IMP administration, the investigator or subinvestigator will perform the withdrawal examinations and follow-up observation stipulated in the protocol, in so far as they do not affect the pregnancy.

8.5.4 Expedited Reporting of Pregnancy

When a female subject or a partner of a male subject is found to be pregnant during the trial, the investigator or subinvestigator will promptly report this to the sponsor orally or by telephone or e-mail (refer to Annex 1, Emergency Contact). The investigator or subinvestigator will then provide any additional information requested by the sponsor.

8.5.5 Follow-up Investigation of Pregnancy

If a female subject becomes pregnant, the investigator or subinvestigator will perform follow-up investigation of the pregnancy up to delivery or the end of pregnancy and report the results of follow-up in writing to the sponsor. When a subject or subject's partner has delivered, it is best that the neonate be observed for at least six months after delivery.

9 Withdrawal of Individual Subjects From the Trial

Any subject may discontinue participation in the trial at any time without medical disadvantage. The investigator or subinvestigator may withdraw a subject from the trial at any time if it is considered necessary for medical treatment of that subject.

9.1 Screen Failure

If a subject is a screen failure, the following information should be recorded in the CRF for screen failure subjects.

Date of investigation (eligibility confirmation), date of informed consent acquisition (from the subject), reason for screen failure.

9.2 Criteria and Procedures for Withdrawal of Individual Subjects

In any of the events listed below, the investigator or subinvestigator will discontinue IMP administration, perform the tests to be performed at withdrawal stipulated in Section 7.1, Schedule and Procedures, and promptly inform the sponsor of the withdrawal (Annex 1, Emergency Contact). The investigator or subinvestigator will record the date and reason for withdrawal in the CRF.

If withdrawal is necessitated by problems with safety, such as the occurrence of an AE or aggravation of the underlying disease, the investigator or subinvestigator will promptly take appropriate measures and perform follow-up of subjects with AEs if necessary (refer to Section 8.4, Follow-up Investigation of Adverse Events.

1) The subject requests to be withdrawn from the trial.
2) The subject experiences an AE making continuation of the trial difficult.
3) Psychosocial therapy other than BRENDA approach is needed (except for the period after the end of the examination of the run-out period).
4) The dose of the IMP needs to be changed.

5) It has been found after the start of the trial that the subject does not meet the inclusion criteria or falls under any of the exclusion criteria.
6) A female subject has become pregnant or been suspected of being pregnant.
7) The investigator or subinvestigator judges that the subject should be withdrawn for other reasons.

9.3 Follow-up Investigation of Subjects Who Do not Visit the Trial Site

If a subject does not visit the trial site for unknown reasons, the investigator or subinvestigator will promptly contact the subject or persons concerned such as the family by telephone or other means to confirm AEs and ask for visit.

If the subject does not visit the trial site, the following will be investigated and recorded in the subject's medical records, etc.

1) The date of investigation
2) The method of investigation
3) Whether or not the subject was contacted
4) Reason why the subject does not (or cannot) visit the trial site
5) Details of IMP compliance
6) Occurrence or non-occurrence of AEs. If an AE has occurred: name of the event, date (and time) of onset and date (and time) of recovery, severity, relationship to the IMP, measures taken regarding IMP administration, treatment of AE, outcome.
7) If follow-up investigation is impossible: the reason why

10 Collection of Case Report Form Data and Specification of Source Data

10.1 Collection of Case Report Form Data

1) Electronic Data Capture (EDC) will be used in the trial.
2) Subject data will be entered directly into the database from the trial site via a Web browser. These data collected by EDC will constitute the CRF. The results obtained from the clinical laboratory test performed by the central laboratory and the ECG analysis results obtained from the central ECG laboratory will be transferred from these facilities directly to the sponsor.
3) Regarding quality assurance of CRFs, the guidelines specified in "Use of Electromagnetic Records and Electronic Signatures in Applications for Approval or Licensing of Drugs" (PFSB Notification No. 0401022, dated 01 Apr 2005) and "Guidance on Electronic Capture of Clinical Study Data" (Drug Evaluation Committee, Japan Pharmaceutical Manufacturers Association, dated 01 Nov 2007) will be observed.

4) For every subject who provides consent to participate in the trial, a CRF will be created on an EDC data entry screen that conforms to the items of CRF data collection described in the trial protocol.
5) The investigator, subinvestigator, or trial associate will create CRFs according to the manual provided by the sponsor. If source documents are available and the objectivity of the data can be ensured, then the data may be recorded in a CRF by a trial associate.
6) When entering data into CRFs from the trial site, a predetermined check will be automatically performed. The investigator, subinvestigator, or a trial associate will make corrections as necessary.
7) The sponsor will verify CRFs in comparison to source documents and conduct data reviews. If additional query is necessary, the sponsor will issue an intra-system query and the investigator, subinvestigator, or a trial associate will perform data correction or provide a response to the sponsor's query as necessary.
8) A history of all revisions made after the initial data entry is saved on the server will be automatically recorded within the system (date and time of revision, name of person making revision, pre- and post-revision data, reason for revision, date and time of query, name of person issuing query, details of query, etc).
9) After completion of all CRF data entry and confirmation that the content is correct and complete, including confirmation of the audit trail, the investigator will attach an electronic signature.
10) Details concerning data collection will be specified in a separate manual prepared in advance.

10.2 Source Documents

1) Source documents are defined as those documents that are the source of data transcribed into CRFs as trial results.
   Medical records and other records (medical records, nursing records, prescription records), registration verification forms, subject screening list, ICFs, clinical laboratory test and other measurement reports, ECG charts, IMP management records, rating scales, and other documents
2) The investigator or the trial site will retain all trial-related documents and records except CRFs in such a manner that enables the sponsor or the regulatory authority to have direct access to the documents and records.
3) The original ICFs will be retained according to the method specified by each trial site.
4) After completion of the trial, the sponsor will retain the original CRFs on CD-ROM or some other appropriate electronic medium and the investigator or the trial site will retain copies.

10.3 Case Report Form Items to Be Treated as Source Data

Not applicable

10.4 Data to Be Collected by the Sponsor

1) CRFs
2) Clinical laboratory results and standard values
3) Analysis results of 12-lead ECG obtained from the central ECG laboratory

11 Statistical Analysis

Details of statistical analyses planned in this trial are described. More detailed description of the statistical analyses will be contained in the statistical analysis plan to be separately prepared.

11.1 Analysis Sets

Both of data from the preceding double-blind lead-in study and this extension study will be summarized and analyzed in the following analysis sets.

- Safety set (SS):
  Subjects who received the IMP at least once in this trial
- Full analysis set (FAS):
  Subjects in the SS who have data of the number of HDDs[d] at baseline in the lead-in study and at one timepoint or more after the initial IMP administration in this trial

11.2 Handling of Data

11.2.1 Baseline and Baseline II

Unless otherwise specified, baseline for the treatment period will be the one in the lead-in study, and baseline in the run-out period and posttreatment observation period (hereinafter referred to as baseline II) will be Week 24 of the treatment period (Visit 10) in this trial.

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[d]The number of HDDs is defined as the number of days per month (days/month) with alcohol consumption per day of > 60 g for males and > 40 g for females. One month is defined as 4 weeks (28 days). The number of HDDs is calculated as the number of days per month with alcohol consumption per day of > 60 g for males and > 40 g for females multiplied by 28 and then divided by the number of days per month without missing data. Data will be considered as missing if the number of days per month without missing data is less than 7 days.

11.2.2 Timepoint of Evaluation and Timepoint of Case Report Form Entry (Nominal Timepoint)

Unless otherwise specified, nominal visits (an assessment is evaluated according to the visit it was intended to happen at with the exception of early withdrawals and unscheduled visits where windowing is used) will be used.

11.2.3 Endpoints Derived by Timeline Followback

The baseline of the endpoints derived by TLFB (eg, number of HDDs and TAC) will be 28 days before the Screening Visit in the lead-in study. Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 of the lead-in study will be 28 days each starting from the Randomization Visit of the lead-in study as Day 1 (eg, Days 1 to 28 for Week 4 and Days 29 to 56 for Week 8). Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 of this trial will be 28 days each starting from Week 0 of this trial (Visit 2 of this trial) as Day 1.

Baseline II will be 28 days before the start of the run-out period (Week 24 of the treatment period, Visit 10 of this trial). The run-out period will be 28 days from the start of the run-out period. However, if the Run-out Period Visit (Visit 11 of this trial) or the Withdrawal Visit after the run-out period comes before the start of the run-out period + 28 days, the period will be from the start of the run-out period to the Run-out Period Visit or Withdrawal Visit.

11.3 Analysis Items and Method

11.3.1 Safety Analysis

Unless otherwise specified, safety analysis will be performed in the SS with data from the lead-in study and this trial.

11.3.1.1 Extent of Exposure

(1) Lead-in study and this trial

Descriptive statistics (number of subjects, mean, standard deviation, minimum, median, maximum; the same statistics hereinafter) will be obtained for the number of days of IMP administration and the proportion of the number of days of IMP administration in the treatment period. Frequency of days when alcohol was consumed without IMP administration will be calculated. Pooled data from the treatment groups will be used for the tabulation regardless of the treatment groups in the lead-in study or treatment groups in the run-out period of this trial.

In subjects in the SS who received nalmefene hydrochloride 20 mg in the lead-in study and the run-out period of this trial, descriptive statistics will be obtained for the number of days of IMP administration and the proportion of the number of days of IMP administration in the treatment period. Frequency of days when alcohol was consumed without IMP administration will be calculated.

(2) Lead-in study and the treatment period of this trial

Descriptive statistics will be obtained by treatment group in the lead-in study (nalmefene hydrochloride 10 mg, nalmefene hydrochloride 20 mg, and placebo groups) for the number of days of IMP administration in the lead-in study and the treatment period of this trial and the proportion of the number of days of IMP administration in the treatment periods. Frequency of days when alcohol was consumed without IMP administration will be calculated.

(3) Treatment period of this trial

Descriptive statistics will be obtained by treatment group in the lead-in study for the number of days of IMP administration in the treatment period of this trial and the proportion of the number of days of IMP administration in the treatment period. Frequency of days when alcohol was consumed without IMP administration will be calculated.

(4) Run-out period of this trial

In subjects in the SS who advanced to the run-out period, descriptive statistics will be obtained by treatment group in the run-out period of this trial (nalmefene hydrochloride 20 mg and placebo groups), for the number of days of IMP administration in the run-out period of this trial and the proportion of the number of days of IMP administration in the treatment period. Frequency of days when alcohol was consumed without IMP administration will be calculated.

11.3.1.2 Adverse Events

(1) AEs in the lead-in study and this trial

Treatment-emergent adverse events will be summarized by system organ class (SOC) and preferred term (PT) as well as “any TEAEs,” and the summaries will provide the number of subjects with TEAEs and incidence of those. Drug-related TEAEs will be summarized in the same manner. Pooled data from the treatment groups will be used for the tabulation regardless of the treatment groups in the lead-in study or treatment groups in the run-out period of this trial.

In subjects in the SS who received nalmefene hydrochloride 20 mg in the lead-in study and the run-out period of this trial, TEAEs will be summarized by SOC and PT as well as "any TEAEs," and the summaries will provide the number of subjects with TEAEs and incidence of those. Tabulation by severity and tabulation by timepoint (lead-in study or this trial) will also be performed. Drug-related TEAEs will be summarized in the same manner.

(2) AEs in the lead-in study and the treatment period of this trial

In each treatment group in the lead-in study, TEAEs will be summarized by SOC and PT as well as "any TEAEs," and the summaries will provide the number of subjects with TEAEs and incidence of those. Tabulation will also be performed by severity and timepoint (in the lead-in study and this trial). Drug-related TEAEs will be summarized in the same manner.

(3) AEs in the run-out period of this trial

In subjects in the SS who advanced to the run-out period of this trial, TEAEs will be summarized by SOC and PT as well as "any TEAEs" for each treatment group in the run-out period of this trial, and the summaries will provide the number of subjects with TEAEs and incidence of those. Tabulation will also be performed by severity. Drug-related TEAEs will be summarized in the same manner.

(4) AEs in the posttreatment observation period of this trial

In subjects in the SS who advanced to the posttreatment observation of this trial, TEAEs will be summarized by SOC and PT as well as "any TEAEs" for each treatment group in the run-out period of this trial, and the summaries will provide the number of subjects with TEAEs and incidence of those. Tabulation will also be performed by severity. Drug-related TEAEs will be summarized in the same manner.

11.3.1.3 Death, Other Serious Adverse Events and Other Significant Adverse Events

In the same manner as AEs, the following AEs will be summarized by SOC and PT as well as "any AEs."

- Serious TEAEs, drug-related serious TEAEs, TEAEs leading to discontinuation, drug-related TEAEs leading to discontinuation in the lead-in study and this trial
- Serious TEAEs, drug-related serious TEAEs, TEAEs leading to discontinuation, drug-related TEAEs leading to discontinuation in the lead-in study and the treatment period of this trial

- Serious TEAEs, drug-related serious TEAEs, TEAEs leading to discontinuation, drug-related TEAEs leading to discontinuation in the run-out period of this trial
- Serious TEAEs, drug-related serious TEAEs, TEAEs leading to discontinuation, drug-related TEAEs leading to discontinuation in the posttreatment observation period of this trial

11.3.1.4 Clinical Laboratory Tests

(1) Clinical laboratory tests in the lead-in study and this trial

Hematology and chemistry at each timepoint will be summarized with descriptive statistics, as well as change from baseline. Urinalysis at each timepoint will be summarized in shift tables from baseline. Potentially clinically significant (PCS) values will also be summarized. Pooled data from the treatment groups will be used for the tabulation regardless of the treatment groups in the lead-in study or treatment groups in the run-out period of this trial.

In subjects in the SS who received nalmefene hydrochloride 20 mg in the lead-in study and the run-out period of this trial, hematology and chemistry at each timepoint will be summarized with descriptive statistics, as well as change from baseline. Urinalysis at each timepoint will be summarized in shift tables from baseline. Potentially clinically significant values will also be summarized.

(2) Clinical laboratory tests in the lead-in study and the treatment period of this trial

Hematology and chemistry at each timepoint will be summarized with descriptive statistics, as well as change from baseline by treatment group in the lead-in study. Urinalysis at each timepoint will be summarized in shift tables from baseline by treatment group in the lead-in study. Potentially clinically significant values will also be summarized by treatment group in the lead-in study.

(3) Clinical laboratory tests in the run-out period and posttreatment observation period of this trial

In subjects in the SS who advanced to the run-out period of this trial, hematology and chemistry at each timepoint will be summarized by treatment group in the run-out period of this trial with descriptive statistics, as well as change from baseline II. Urinalysis at each timepoint will be summarized by treatment group in the run-out period of this trial in shift tables from baseline II. Potentially clinically significant values will also be summarized by treatment group in the run-out period of this trial.

11.3.1.5 Vital Signs and Body Weight

In the same manner as for clinical laboratory tests regarding "subjects, treatment group, and baseline," vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) and body weight at each timepoint of the following periods will be summarized with descriptive statistics, as well as change from baseline.

In the same manner, PCS values will be summarized in the following periods.

- Vital signs and body weight in the lead-in study and this trial
- Vital signs and body weight in the lead-in study and the treatment period of this trial
- Vital signs and body weight in the run-out period and posttreatment observation period of this trial

11.3.1.6 Twelve-lead Electrocardiogram

In the same manner as for clinical laboratory tests regarding "subjects, treatment group, and baseline," heart rate, RR interval, PR interval, QRS interval, QT interval, QTcB, and QTcF at each timepoint of the following periods will be summarized with descriptive statistics, as well as change from baseline.

In the same manner, a shift table of "Abnormal Significant," "Abnormal Insignificant," or "Normal" at each timepoint of the following periods from baseline will be provided.

In the same manner, PCS values will be summarized in the following periods.

In the same manner, QTcB/QTcF at each timepoint of the following periods and worst QTcB/QTcF will be categorically summarized. Categories will be > 450 msec, > 480 msec, and > 500 msec. Change in QTcB/QTcF from baseline at each timepoint and worst QTcB/QTcF will be categorically summarized. Categories will be > 30 msec and > 60 msec.

- 12-lead ECG in the lead-in study and this trial
- 12-lead ECG in the lead-in study and the treatment period of this trial
- 12-lead ECG in the run-out period and posttreatment observation period of this trial

11.3.1.7 Physical Examination

In the same manner as for clinical laboratory tests regarding "subjects, treatment group, and baseline," the physical examinations will be categorically summarized by timepoint

of the following periods. Categories will be "Abnormal Significant," "Abnormal Insignificant," and "Normal."

- Physical examinations in the lead-in study and this trial
- Physical examinations in the lead-in study and the treatment period of this trial
- Physical examinations in the run-out period and posttreatment observation period of this trial

11.3.1.8 Profile of Mood States

In the same manner as for clinical laboratory tests regarding "subjects, treatment group, and baseline," TMD score and factors (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment) in the following periods will be summarized with descriptive statistics, as well as the changes from baseline.

- POMS in the lead-in study and this trial
- POMS in the lead-in study and the treatment period of this trial
- POMS in the run-out period and posttreatment observation period of this trial

For TMD score in the lead-in study and the treatment period of this trial, mixed model for repeated measures (MMRM) analysis will be performed for the changes from baseline in the same manner as the analysis of the number of HDDs.

11.3.1.9 Columbia-Suicide Severity Rating Scale

(1) Subjects, treatment group, and period

In the same manner as for clinical laboratory tests regarding "subjects, treatment group, and baseline," C-SSRS in the following periods will be summarized as shown in (2) below.

- C-SSRS in the lead-in study and this trial
- C-SSRS in the lead-in study and the treatment period of this trial
- C-SSRS in the run-out period and posttreatment observation period of this trial

(2) Items and method of tabulation

The following outcomes are C-SSRS categories and have binary responses (yes/no). The Category 1 to 10 will be summarized in each treatment group at each timepoint.

- Category 1 − Wish to be Dead
- Category 2 − Non-specific Active Suicidal Thoughts

- Category 3 − Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 − Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 − Active Suicidal Ideation with Specific Plan and Intent
- Category 6 − Preparatory Acts or Behavior
- Category 7 − Aborted Attempt
- Category 8 − Interrupted Attempt
- Category 9 − Actual Attempt (non-fatal)
- Category 10 − Completed Suicide

The following is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no). This outcome will also be summarized in each treatment group at each timepoint.

- Self-injurious behavior without suicidal intent

The following variables will be derived using the above categories. These variables will also be summarized in each treatment group.

- Suicidal ideation (1 to 5)
  A "yes" answer at any post-baseline visit to any one of the five suicidal ideation questions (Categories 1 to 5) on the C-SSRS.
- Suicidal behavior (6 to 10)
  A "yes" answer at any post-baseline visits to any one of the five suicidal behavior questions (Categories 6 to 10) on the C-SSRS.
- Suicidal ideation or behavior (1 to 10)
  A "yes" answer at any post-baseline visits to any one of the ten suicidal ideation and behavior questions (Categories 1 to 10) on the C-SSRS.
- Treatment-emergent suicidal ideation
  An increase in the maximum suicidal ideation score[e] at post-baseline visits from the suicidal ideation category at baseline.
- Treatment-emergent serious suicidal ideation
  An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS at

[e]Suicidal ideation score: The maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation is present.
0 = No Suicidal Ideation, 1 = Wish to be Dead, 2 = Non-specific Active Suicidal Thoughts, 3 = Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act, 4 = Active Suicidal Ideation with Some Intent to Act, without Specific Plan, 5 = Active Suicidal Ideation with Specific Plan and Intent

post-baseline visits from not having serious suicidal ideation (scores of 0 to 3) at baseline.

- Emergence of serious suicidal ideation
  An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS at post-baseline visits from no suicidal ideation (scores of 0) at baseline.
- Emergence of suicidal behavior
  The occurrence of suicidal behavior at post-baseline visits from not having suicidal behavior at screening or baseline in the lead-in study.

In each treatment group, Maximum Suicidal ideation score at post-baseline visits will be summarized in shift tables from Suicidal ideation score at baseline.

The following C-SSRS category will be derived and it will be summarized in shift tables from baseline in each treatment group at each timepoint.

- C-SSRS category
  "No suicidal ideation or behavior," "suicidal ideation," and "suicidal behavior"

11.3.1.10 Dependence Survey

Answers to questions of dependence survey A at the end of the run-out period and questions of dependence survey B at the end of the posttreatment observation will be summarized by treatment group in the run-out period of this trial.

11.3.2 Efficacy Analysis

The following efficacy analyses will be performed in the FAS.

11.3.2.1 Number of Heavy Drinking Days

The number of HDDs at each timepoint of the lead-in study and the treatment period of this trial will be summarized with descriptive statistics, as well as change from baseline by treatment group in the lead-in study (nalmefene hydrochloride 10 mg, nalmefene hydrochloride 20 mg, and placebo groups).

In subjects in the FAS who advanced to the run-out period of this trial, the number of HDDs in the run-out period of this trial will be summarized with descriptive statistics by treatment group in the run-out period of this trial (nalmefene hydrochloride 20 mg and placebo groups), as well as change from baseline II.

As an exploratory analysis, MMRM analysis will be performed for the changes in the number of HDDs from baseline at each timepoint of the lead-in study and the treatment period of this trial. The baseline will be the one in the lead-in study. Analyses will

include the fixed, categorical effects of treatment in the lead-in study, sex, timepoint (Weeks 4, 8, 12, 16, 20, and 24 of the lead-in study and Weeks 4, 8, 12, 16, 20, and 24 of this trial), and treatment-by-timepoint interaction as well as the continuous, fixed covariates of baseline number of HDDs, and baseline number of HDDs-by-timepoint interaction. An unstructured (co)variance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

As an exploratory analysis, in subjects in the FAS who advanced to the run-out period of this trial, changes in the number of HDDs from baseline II in the run-out period of this trial will be analyzed by using an analysis of covariance (ANCOVA) model with treatment and sex in the run-out period of this trial as fixed, categorical effect and number of HDDs at baseline II as covariance.

11.3.2.2 Total Alcohol Consumption

Total alcohol consumption will be summarized with descriptive statistics, and exploratory MMRM analysis and ANCOVA will be performed in the same manner as with the number of HDDs.

11.3.2.3 Response Shift Drinking Risk Level

Frequency of RSDRL at each timepoint of the lead-in study and the treatment period of this trial will be calculated by treatment group in the lead-in study.

In subjects in the FAS who advanced to the run-out period of this trial, frequency of RSDRL in the run-out period of this trial will be calculated by treatment group in the run-out period of this trial.

Observed case data will be analyzed without imputation of missing values. Furthermore, analyses will be performed in the entire FAS and all subjects in the FAS who advanced to the run-out period, where missing values will be handled as non-responders.

11.3.2.4 Response Low Drinking Risk Level

In the same manner as with RSDRL, frequency of RLDRL at each timepoint will be calculated.

11.3.2.5 70% Total Alcohol Consumption Responder Rate

In the same manner as with RSDRL, frequency of 70% TAC responder rate at each timepoint will be calculated.

11.3.2.6 Heavy Drinking Day Responder Rate

In the same manner as with RSDRL, frequency of HDD responder rate at each timepoint will be calculated.

11.3.2.7 Clinical Global Impression-Severity of Illness

In the same manner as the number of HDDs, CGI-S will be summarized with descriptive statistics, and exploratory MMRM analysis will be performed.

11.3.2.8 Clinical Global Impression-Global Improvement

In the same manner as the number of HDDs, CGI-I will be summarized with descriptive statistics, and exploratory MMRM analysis will be performed. However, the scores at each timepoint will be analyzed as opposed to change from baseline since the score itself is an assessment of change from baseline. The CGI-S at baseline will be included for covariate adjustment.

11.3.2.9 SF-36 Subscales (Physical Functioning, Physical Role Functioning, Bodily Pain, General Health Perceptions, Vitality, Mental Health, Emotional Role Functioning, and Social Role Functioning), Physical Component Summary, and Mental Component Summary

For SF-36 subscales and each Component Summary, descriptive statistics will be obtained in the same manner as the number of HDDs, and exploratory MMRM analysis will be performed.

11.3.2.10 EuroQol 5 Dimension Utility Score and EuroQol 5 Dimension Visual Analog Scale

For EQ-5D Utility score and EQ-5D VAS, descriptive statistics will be obtained in the same manner as the number of HDDs, and exploratory MMRM analysis will be performed.

11.3.2.11 Alcohol Quality of Life Scale

For each domain and item of AQoLS, descriptive statistics will be obtained in the same manner as the number of HDDs, and exploratory MMRM analysis will be performed.

11.3.2.12 Resource Use Measurement Questionnaire-Alcohol Dependence

Frequency will be calculated for each item in sociodemographic, resource consumption, and sick leaves at each timepoint of the lead-in study and the treatment period of this trial by treatment group in the lead-in study.

In subjects in the FAS who advanced to the run-out period of this trial, frequency will be calculated for each item in sociodemographic, resource consumption, and sick leaves in the run-out period of this trial by treatment group in the run-out period of this trial.

11.3.2.13 Gamma-glutamyl Transferase

Log-transformed GGT will be summarized with descriptive statistics, and exploratory MMRM analysis will be performed in the same manner as the number of HDDs. The model includes the fixed, categorical effects of treatment, sex, timepoint, and treatment-by-timepoint interaction as well as the continuous, fixed covariates of log-transformed baseline values, and log-transformed baseline values-by-timepoint interaction.

11.3.2.14 Alanine Aminotransferase

For log-transformed ALT, descriptive statistics will be obtained, and exploratory MMRM analysis will be performed in the same manner as the analysis of GGT.

11.3.3 Disposition of Subjects

Disposition of subjects will be summarized. The disposition includes the number of subjects who advanced to this trial, the number of subjects who advanced to the run-out period, the number of subjects who completed the trial, and the number of subjects who withdrew from the trial.

The number of subjects who withdrew from the trial will be obtained by primary reason for withdrawal.

11.3.4 Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be summarized by treatment group in the lead-in study for the FAS and SS.

In subjects in the FAS and SS who advanced to the run-out period of this trial, the following demographic and other baseline characteristics will be summarized by treatment group in the run-out period of this trial.

- Age
- Sex
- Height
- Body weight
- Body mass index
- Medical history and complications
- Alcohol drinking history

- Smoking history
- Drug abuse history
- Prior drugs and therapies
- Concomitant drugs
- Revised Clinical Institute Withdrawal Assessment for Alcohol

11.4 Procedures for Reporting Deviations From the Original Statistical Analysis Plan

If any change is made to the analysis method planned in the protocol when the statistical analysis plan is finalized, the content and the reason for the change will be described in the statistical analysis plan and the clinical study report.

11.5 Rationale for Sample Size Determination

The targeted subjects in this trial are the subjects who complete the preceding Study 339-14-001 and wish to participate in this trial. The estimate number of subjects is approximately 400.

Based on the completion rate (nalmefene 20 mg group: 0.53 and placebo group: 0.67) in patients with a high or very high DRL at baseline and at randomization in Study 12013A (the duration of treatment: 52 weeks), the continuation rate of the completers in the preceding Study 339-14-001 to this trial was estimated to be 0.8.

12 Quality Control and Quality Assurance for the Trial

To ensure quality of the trial, trial sites, contract research organizations, laboratories performing clinical tests, the DNA storage facility, and the sponsor will perform quality control for the trial according to their respective Standard Operating Procedures.

The audit division of the sponsor company will carry out audits within the company and, as necessary, at the trial site and contract research organizations or organizations entrusted to perform related activities, and check whether quality control of the trial is appropriately performed according to the Standard Operating Procedures.

13 General Items of Caution Pertaining to the Trial

13.1 Ethics and GCP Compliance

This clinical trial is to be conducted in compliance with the ethical principles of the Declaration of Helsinki, the Pharmaceutical Affairs Law, the Ordinance on Good Clinical Practice (GCP) (Ministry of Health and Welfare Ordinance No. 28 dated 27 Mar 1997), relevant notifications, and this trial protocol.

13.2 Institutional Review Board

Prior to performance of this trial, the appropriateness of performance of this trial will be reviewed from ethical, scientific, and medical perspectives by the IRB designated by the trial site, and this trial will be commenced only after obtaining the approval of the IRB.

13.3 Subject Consent

13.3.1 Procedures for Obtaining Consent

1) Prior to the start of IMP administration, the investigator or subinvestigator will fully explain the matters listed in Section 13.3.2 to each subject who will be included in the trial, using the ICF, and give the ICF to the subject. The subject will be provided sufficient time to make a decision regarding participation. After confirming that the subject has properly understood the explanation, the investigator or subinvestigator will obtain written voluntary consent for participation in the trial from the subject.
2) The investigator or subinvestigator who has provided the explanation and the subject will each put their printed name and personal seal or signature on the ICF, and write the date on which they sign or stamp the form. If a trial associate has provided a supplemental explanation of the trial, he/she will also put his/her printed name and personal seal or signature on the form and write the date on which he/she signs or stamps the form.
3) The original of the ICF that was signed or stamped and dated will be retained by the investigator or subinvestigator according to the regulations of the trial site. A copy of the original ICF will be given to the subject.
4) After obtaining informed consent from a subject, the investigator or subinvestigator will write the date of informed consent acquisition and subject identification code in the documents for enrolled subjects (list of screened subjects and list of enrolled subjects).
5) If new information becomes available that may influence the willingness of the subject to continue participation in the trial, the investigator or subinvestigator will promptly inform the subject of such information and confirm the willingness of the subject to continue participation in the trial, and then record the result in the

subject's medical records. If there is guidance regarding the recording of re-consent stipulated by the trial site, it will be followed.

13.3.2 Contents of Informed Consent Form

1) An explanation that the trial involves research
2) The type of IRB that reviews the appropriateness of trial conduct, matters to be reviewed by the IRB, and other relevant descriptions of the activity of the IRB
3) The objectives of the trial
4) The trial procedures (including research-related aspects of the trial, inclusion criteria for subjects, and, if random allocation is performed, the probability of randomization to each treatment arm)
5) The expected duration of the subject's participation in the trial
6) The planned number of subjects involved in the trial
7) The foreseeable IMP-related physical and mental benefits (if no benefits are expected, this should be indicated) as well as risks or inconveniences to the subject
8) The existence of alternative treatments for the subject, and their important potential benefits and risks
9) The treatment and compensation available to the subject in the event of trial-related injury to health
10) An explanation that the subject's participation in the trial is voluntary, and that the subject can refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which he or she would otherwise be entitled
11) An explanation that the subject will be informed in a timely manner if information becomes available that may be relevant to his or her willingness to continue participation in the trial
12) The circumstances or reasons under which the subject's participation in the trial should be terminated
13) An explanation that the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records without violating the confidentiality of the subject, and that by signing the ICF, the subject is authorizing such access
14) An explanation that if the results of the trial are published, the subject's identity will remain confidential
15) The anticipated expenses to the subject for participating in the trial
16) The anticipated payment, if any, to the subject for participating in the trial (agreements on payment, etc)
17) The name, position, and contact address of the investigator or subinvestigator

18) The persons at the trial site to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury to health
19) Matters to be observed by subjects

13.3.3 Amendments to the Informed Consent Form

If revision of the ICF becomes necessary due to newly obtained information, the investigator will promptly revise the ICF to include that information after conferring with the sponsor.

The investigator, when revising the ICF, will report this to the head of the trial site and submit the revised document to the IRB designated by the trial site to obtain its approval.

If new information becomes available that may influence the willingness of subjects to continue participation in the trial and the ICF has been revised according to the new information, the investigator or subinvestigator will again obtain subjects' written informed consent to continue participation in the trial.

13.4 Management of Investigational Medicinal Products

1) The sponsor will issue the "Procedures for Handling of Investigational Medicinal Products" to the persons designated by the trial site.
2) The sponsor will issue the "Document on Investigational Medicinal Products Storage Conditions" to the investigator or subinvestigator, trial associates, and IMP manager.
3) The sponsor will deliver the IMPs to the trial site following the start of the trial period contracted with the trial site.
4) The IMP manager will manage the IMPs appropriately according to the "Procedures for Handling of Investigational Medicinal Products" prepared by the sponsor.
5) The IMP manager will prepare and retain the "Record of Management and Storage of Investigational Medicinal Products."

13.5 Direct Access to Source Documents and Monitoring

13.5.1 Direct Access to Source Documents

The head of the trial site and the investigator must accept monitoring and audits to be performed by the sponsor and inspection by the IRB and Japanese and foreign regulatory authorities, and must make source documents and all other trial-related records available

to these agencies for direct access (including copying). Subjects authorize such direct access by signing the written ICF.

13.5.2 Monitoring

The sponsor bears responsibility for ethical, legal, and scientific conduct of the trial. The sponsor will perform monitoring according to the "Procedures for monitoring" specified for this trial. Monitoring includes periodic visits, phone calls, or other contact with the trial site for the provision, obtaining, and recording of updated trial-related information by monitors designated by the sponsor.

The sponsor may entrust a portion of monitoring activity to a contract research organization.

13.5.3 Documents to Be Retained by the Investigator

The trial-related documents to be retained by the investigator will be kept in the investigator's file, which will be managed by the investigator.

13.6 Deviations From and Changes or Amendments to the Trial Protocol

13.6.1 Deviations From the Trial Protocol

1) The investigator or subinvestigator should not deviate from the protocol or change it without prior written agreement between the investigator and the sponsor and the written approval of the IRB of the trial site based on prior review.
2) In unavoidable medical circumstances such as the need to avoid emergent risk to a subject, the investigator or subinvestigator may deviate from the protocol or change the protocol without prior written agreement from the sponsor and prior approval of the IRB. In such an event, the investigator will promptly submit a document providing the details of and reason for the deviation or change to the sponsor and the head of the trial site and obtain approval from the IRB. In addition, the investigator will obtain written approval from the head of the trial site and the written agreement of the sponsor by way of the head of the trial site.
3) The investigator or subinvestigator will record all deviations from the protocol.

13.6.2 Amendments to the Trial Protocol

1) The investigator will promptly submit to the sponsor, the head of the trial site, and the IRB by way of the head of the trial site, a written report on any changes in the trial that may significantly affect conduct of the trial or increase risks to the trial subjects.

2) The sponsor, after conferring with the investigator, will agree with the investigator on the contents of the revised protocol and compliance with the revised protocol.
3) The sponsor will promptly submit the revised protocol to the head of the trial site.

13.7 Archiving of Records

1) The trial site will retain all the trial-related documents and records for the period of time indicated in a) or b) below, whichever is longer. However, if the sponsor requires a longer period of archiving, the head of the trial site will consult with the sponsor on the period and procedures of record retention.
   a) The date an Application for Approval of a Pharmaceutical Product for the IMP is granted; or, if the head of the trial site receives notification from the sponsor that development has been terminated or that results of the trial will not be submitted with the approval application, the date 3 years after receipt of such notification.
   b) The date 3 years after termination or completion of the trial.
2) The investigator will retain the trial-related documents and records as directed by the head of the trial site.
3) If it becomes no longer necessary to retain the trial-related documents and records at the trial site, the sponsor will notify the head of the trial site.

13.8 Termination or Interruption of Part or All of the Trial

13.8.1 Termination or Interruption of the Trial at Individual Trial Sites

1) In the event of termination or interruption of the trial, the investigator will promptly provide the head of the trial site with written notification and a written explanation of the details of the termination or interruption of the trial.
2) When the sponsor has been informed by the head of a trial site that the investigator has terminated or interrupted the trial, the sponsor will obtain a detailed written explanation of the termination or interruption of the trial from the head of the trial site.

13.8.2 Termination or Interruption of the Entire Trial

1) When the entire trial is to be terminated or interrupted by the sponsor, the sponsor will promptly provide the heads of all trial sites involved in the trial and the regulatory authority with written notification and a detailed written explanation of the reason for the termination or interruption of the trial.
2) When the investigator has received notification of termination or interruption of the entire trial by the sponsor from the head of the trial site, the investigator will obtain a detailed written explanation of the termination or interruption of the trial from the head of the trial site, promptly notify the trial subjects currently receiving

IMP administration, and take necessary measures such as switching to appropriate alternative treatment(s).

3) When development of the IMP is terminated by the sponsor, the sponsor will promptly provide the heads and the investigators of all trial sites involved in the trial and the regulatory authority with written notification and a detailed written explanation of the reason for the termination of development.

13.9 Protection of Subjects' Personal Information

In completion and handling of CRFs, the investigator and subinvestigator will take adequate care to ensure protection of the personal information of subjects. Individual subjects will be identified by subject numbers and subject identification codes. The sponsor will not provide the information obtained to any third party.

13.10 Compensation for Injury to Health

Trial subjects will be compensated for health damages according to the criteria established by the trial sponsor with reference to the "Guidelines for Health Damage Compensation to Trial Subjects" (revised 25 Nov 2009) of the Japan Pharmaceutical Industry Legal Affairs Association.

13.11 Agreement on Publication

The sponsor may use the findings obtained from this trial for purposes such as an "Application for Approval of a Pharmaceutical Product" for the IMP.

When the results of this trial and relevant data are to be published in scientific journals or at academic meetings, the investigator will obtain prior written approval from the sponsor.

14 Trial Administrative Structure

The administrative structure of this trial is shown in Annex 1, Annex 2, and Annex 3.

15 Scheduled Duration of the Trial

From 05 Dec 2014 to 31 Mar 2018

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