STATISTICAL ANALYSIS PLAN

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

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

Statistical Analysis Plan

Protocol No.: 339-14-002

Confidential

(Translated Version)

Otsuka Pharmaceutical Co., Ltd.

Version 1: 27 Mar 2017

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List of Abbreviations and Definition of Terms

List of Abbreviations

Abbreviation	Expansion or Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AQoLS	Alcohol Quality of Life Scale
BMI	Body Mass Index
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-I	Clinical Global Impression-Global Improvement
CGI-S	Clinical Global Impression-Severity of Illness
CIWA-Ar	Revised Clinical Institute Withdrawal Assessment For Alcohol
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DRL	Drinking Risk Level
EQ-5D	EuroQol 5 Dimension
FAS	Full Analysis Set
γ-GTP	Gamma-glutamyl transpeptidase
HDD	Heavy Drinking Day
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities ICH
MMRM	Mixed model for repeated measures approach
OC	Observed Case
PCS	Potentially clinically significant
POMS	Profile of Mood States
QTc	Corrected QT interval
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
SAS	Statistical Analysis System
SD	Standard deviation
SE	Standard Error
SF-36	MOS 36-item Short-form Health Survey
SS	Safety Set
TAC	Total Alcohol Consumption
TEAE	Treatment-emergent adverse event
TLFB	Timeline Followback
TMD	Total mood disturbance

Abbreviation	Expansion or Definition
VAS	Visual analog scale
WHO	World Health Organization

Definitions of Terms

Term	Definition
Descriptive statistics	Number of subjects, mean, standard deviation, minimum, median, maximum
Frequency	Number of subjects, proportion
Percentile	10th percentile, 25th percentile, 75th percentile, 90th percentile

1 Introduction

This statistical analysis plan describes the detailed statistical analysis methods planned for Study 339-14-002.

This statistical analysis plan is prepared based on the protocol of the trial version 2 (prepared on 20 Nov 2014) of the trial.

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 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.

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 post-treatment observation period. The duration of investigational medicinal product (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 sub-investigator will fully explain the details of this trial to, and obtain written informed consent from, each subject by the end of the treatment period of Study 339-14-001.

In the treatment period, subjects will receive nalmefene hydrochloride 20 mg. Each subject will be instructed to take the IMP orally as needed on days when the subject perceives a risk of drinking alcohol, 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 a ratio of 1:1. Each subject will be instructed to take the IMP orally as needed on days when the subject perceives a risk of drinking alcohol, 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 post-treatment 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, post-treatment observation will be performed only in the subjects who complete the run-out period.

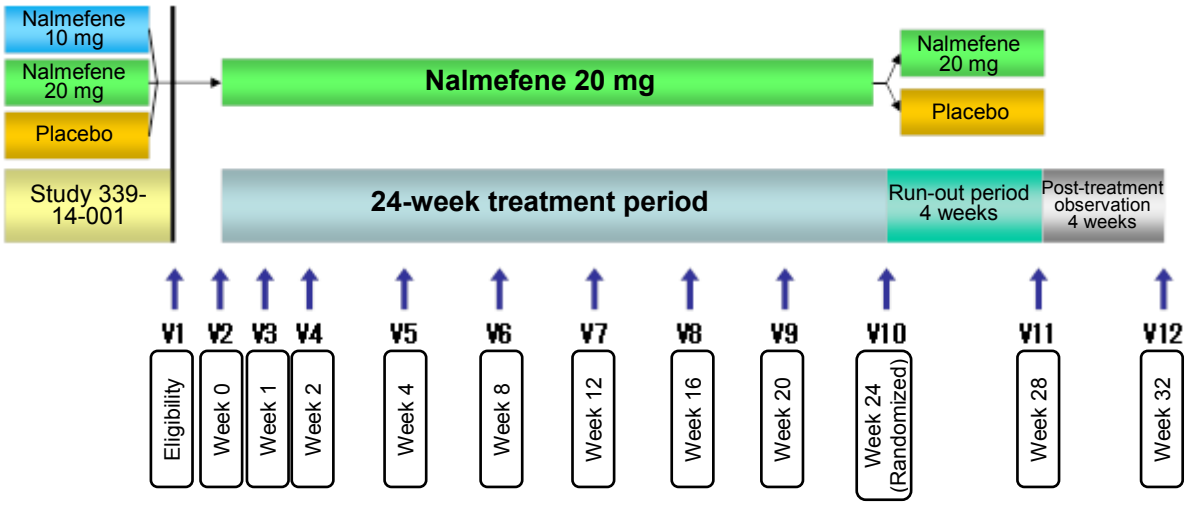

Figure 3-1 Summary of Trial Design

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

4 Implementation of Planned Analyses

The final analysis will be performed using locked data after unblinding.

5 Analysis Sets

5.1 Analysis Sets

The analysis sets in this trial consist of the "safety set" and the "full analysis set."

5.1.1 Safety Set (SS)

Subjects who receive the IMP at least once in this trial

5.1.2 Full Analysis Set (FAS)

Subjects in the SS who have data of the number of HDDs[a] at baseline of Study 339-14-001 (hereinafter referred to as the lead-in study), and at one timepoint or more after the initial IMP administration in this trial

[a] 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 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.

6 Data Analysis Considerations

6.1 Software

Data will be tabulated and analyzed using SAS (SAS Institute Japan Ltd.). SAS released version 9.4 or later will be used.

6.2 Dictionary

Adverse events and complications will be coded using MedDRA (Ver 19.0). Prior and concomitant drugs will be coded using the WHO Drug Dictionary (March 2015 version).

6.3 Data Conversion and Calculation

6.3.1 Baseline and Baseline II

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

6.3.2 Endpoints Derived by Timeline Followback (TLFB)

The number of HDDs and TAC will be derived based on the alcohol consumption data collected with TLFB. Alcohol consumption data will be collected in units of drinks. One drink is defined as consumption of approximately 10 g of pure alcohol, and alcohol consumption will be calculated by multiplying the number of drinks by 10.

The baseline for the endpoints will be the 28-day period 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 (e.g., 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 the day of the Week 0 visit (Visit 2) of this trial as Day 1.

Baseline II will be the 28-day period before the start of the run-out period. The run-out period will be 28 days from the start of the run-out period. However, if the Run-out Period Visit 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 day before the Run-out Period Visit, or the day before the Withdrawal Visit.

The number of HDDs and TAC at the relevant timepoint will be considered as missing, if the number of days per month without missing data is less than 7 days.

When alcohol consumption data on the day of TLFB is collected at the withdrawal examination, the data on the day of withdrawal examination will be handled as missing.

6.3.2.1 Number of Heavy Drinking Days (HDDs)

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 divided by the number of days per month without missing data.

6.3.2.2 TAC

TAC is calculated as the total of daily alcohol consumption per month divided by the number of days per month without missing data.

6.3.3 DRL

DRL at each timepoint will be determined based on risk levels defined by the WHO based on average volume of alcohol consumption per day (criteria for risk of acute problems) using TAC.

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

6.3.4 RSDRL

A downward shift in DRL of 2 categories or more[b]

6.3.5 RLDRL

A low DRL or below

6.3.6 70% TAC Responder Rate

The percentage of subjects whose TAC is reduced by ≥ 70% from baseline

6.3.7 HDD Responder Rate

The percentage of subjects in whom the number of HDDs is ≤ 4

6.3.8 CGI-I and CGI-S

An assessment of "0. Not assessed" will be handled as missing.

6.3.9 SF-36 Subscales and Summary Scores

The data will be calculated according to the method described in Manual of SF-36v2 Japanese version (2004)[1]. However, when an item included in any of the subscales is missing, the missing value will not be imputed and the subscale including the missing item will not be calculated. Component summaries will be calculated using the "factor coefficient based on the 1995 Japanese survey." If at least one of the 8 subscales is missing, component summaries will not be calculated.

6.3.10 Derivation of EQ-5D Utility Score

EQ-5D Utility score will be obtained based on Estimating an EQ-5D population value set: The case of Japan (2002)[2]. The plain main effects model will be used.

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[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

6.3.11 AQoLS Total Score

Each AQoLS item will be scored as “not at all: 0”, “a little: 1”, “quite a lot: 2, or “very much: 3” and the AQoLS total score will be calculated. If at least one item is missing, the total score will not be calculated.

Total Mood Disturbance (TMD) Score and Each Factor in POMS

The TMD score and each factor will be calculated based on Protocol Appendix 7. The TMD score will be obtained by adding the values for each factor (except for the "vigor-activity" value, which will be subtracted).

6.4 Handling of Timepoint

Unless otherwise specified, the timepoint of case report form entry (nominal timepoint) will be used.

6.4.1 Baseline

The periods are described in 6.3.1 Baseline and Baseline II.

6.4.2 Final Assessment

The last data of the assessment in the treatment period after the day of Week 0 visit of this trial (the day of the measurement of the breath alcohol concentration at Visit 2 of this trial), including early withdrawals and unscheduled visits.

6.4.3 Withdrawal Examination

For the efficacy endpoints and POMS, if the day of the withdrawal examination in the treatment period is included in the time window in Table 6.4-1, and there is no data for the timepoint of case report form entry, the data at withdrawal examination will be used as the data at the timepoint of assessment. For the withdrawal examination in the run-out period, the data will be used as the data at Week 28, regardless of the examination day. For the withdrawal examination in the post-treatment observation period, the data will be used as the data at Week 32, regardless of the examination day.

Table 6.4-1 Time Window

Week	Day	Time Window	
		CGI-S, CGI-I	SF-36, EQ-5D, AQoLS, RUMQ-ADP and POMS
Week 0	1	-	-
Week 1	8	2 - 11	-
Week 2	15	12 - 22	-
Week 4	29	23 - 43	-
Week 8	57	44 - 71	
Week 12	85	72 - 99	2 - 127
Week 16	113	100 - 127	
Week 20	141	128 - 155	
Week 24	169	156 - 183	128 - 183

Day 1 (reference day) is the day of Week 0 visit of this trial (the day of the measurement of the breath alcohol concentration at Visit 2 of this trial).

6.4.4 Reference Day of Visit and Timepoints

6.4.4.1 Reference Day of Visit

The day of the Randomization Visit of the lead-in study is the day of inclusion/exclusion assessment at Week 0 of the lead-in study.

The day of Week 0 visit of this trial is the day of the measurement of the breath alcohol concentration at Week 0 (Visit 2 of this trial).

The day of the start of the run-out period is the day of the randomization at Week 24 (Visit 10 of this trial).

The day of the Run-out Period Visit is the day of the measurement of the breath alcohol concentration at Week 28 (Visit 11 of this trial).

The day of the post-treatment observation period visit is the day of the measurement of the breath alcohol concentration at Week 32 (Visit 12 of this trial).

6.4.4.2 Treatment Period

The treatment period of this trial will be from Week 0 visit of this trial to the day before the start of the run-out period.

The lead-in study and the treatment period of this trial will be from the Randomization Visit of the lead-in study to the day before the start of the run-out period. However, the examination data entered at the timepoint of case report form entry at Week 24 (Visit 10 of this trial) will be used as the data in the treatment period.

In case of withdrawal prior to the start of the run-out period (withdrawal in the treatment period, withdrawal prior to the randomization of this trial), the treatment period will be up to the final day of the withdrawal examination. If no withdrawal examination is performed, it will be up to the day of decision of the withdrawal.

6.4.4.3 Run-out Period

The run-out period is defined only for the subjects who complete the treatment period of this trial (those who advance to the run-out period).

The run-out period of this trial will be from the start of the run-out period to the day before the Run-out Period Visit.

However, the examination data entered at the timepoint of case report form entry at Week 28 (Visit 11 of this trial) will be used as the data in the run-out period.

In case of withdrawal prior to the Run-out Period Visit (withdrawal in the run-out period, subjects who do not measure the breath alcohol concentration at Week 28 [Visit 11] of this trial), the run-out period will be up to the final day of the withdrawal examination. If no withdrawal examination is performed, it will be up to the day of decision of the withdrawal.

6.4.4.4 Post-treatment Observation Period

The post-treatment observation period is defined only for the subjects who complete the run-out period of this trial (those who advance to the post-treatment observation period and made the scheduled Run-out Period Visit [Visit 11]).

The post-treatment observation period will be from the Run-out Period Visit to the Post-treatment Observation Visit.

In case of withdrawal prior to the Post-treatment Observation Visit, the post-treatment observation period will be up to the final day of the withdrawal examination. If no withdrawal examination is performed, it will be up to the day of decision of the withdrawal.

6.5 Handling of Missing Values and Outliers

Handling of missing values at the time of derivation of each endpoint is shown in "6.3 Data Conversion and Calculation." Imputation of missing values at the time of analysis is described in the analysis section for each endpoint.

6.6 Significance Level and Confidence Coefficient

The significance level will be 5% (two-sided), and the confidence coefficient will be 95% (two-sided).

6.6.1 Multiple Comparison/Multiplicity

Efficacy endpoints will be tested but not adjusted for multiplicity due to the exploratory nature of the analysis.

7 Disposition of Subjects

7.1 Details of Subject Disposition

For the subjects who provide informed consent to this trial, the number of subjects providing informed consent, the number of subjects advancing to this trial, the number of subjects withdrawing before advancing to this trial, and the number of subjects withdrawing after advancing to this trial but before the IMP administration will be obtained for the entire population and for each treatment group of the lead-in study (the entire groups receiving nalmefene hydrochloride and each treatment group). Subjects who withdraw prior to advancing to this trial and subjects who withdraw after advancing to this trial but before the IMP administration will be tabulated by reason for withdrawal.

For the subjects who advance to this trial, the number of subjects advancing to this trial and the number of subjects receiving the IMP will be obtained for the entire population and for each treatment group of the lead-in study.

For the subjects who receive the IMP (SS), the number of subjects advancing to the run-out period (the number of subjects completing the treatment period) and the number of subjects withdrawing during the treatment period, and their respective proportions will be obtained for the entire population and for each treatment group of the lead-in study. The number of subjects who withdraw during the treatment period and its proportion will be obtained by primary reason for withdrawal. In addition, frequency of the respective primary reasons for withdrawal will be tabulated by timepoint of withdrawal. The timepoints of withdrawal in frequency tabulation will be the same as the respective Weeks (Weeks 4, 8, 12, 16, 20 and 24) of this trial after baseline of the endpoints derived from TLFB.

For the subjects in the SS who advance to the run-out period, the number of subjects receiving the IMP during the run-out period, the number of subjects withdrawing during the run-out period, the number of subjects advancing to the post-treatment observation period (the number of subjects completing the run-out period), the number of subjects withdrawing during the post-treatment observation period, and the number of subjects completing the post-treatment observation period (the number of subjects completing the trial), and their respective proportions will be obtained for the entire population and for each treatment group of the run-out period. The number of subjects who withdraw during the run-out period and the number of subjects who withdraw during the post-treatment observation period, and their respective proportions will be obtained by primary reason for withdrawal.

7.2 Analysis Sets

For the subjects who advance to this trial, the number of subjects included in the SS and subjects included in the FAS, the number of subjects not included in the SS and subjects not included in the FAS, and their respective proportions will be obtained for the entire population and for each treatment group of the lead-in study (the entire groups receiving nalmefene hydrochloride and each treatment group). For the included subjects, the number of subjects advancing to the run-out period and its proportion, and the number of subjects advancing to the post-treatment observation period and its proportion will be obtained for the entire population and for each treatment group of the run-out period.

8 Description of Analysis Sets

8.1 Demographic and Other Baseline Characteristics

For the SS and FAS, the demographic and other baseline characteristics shown in Table 8.1-1, Table 8.1-2, and Table 8.1-3 will be summarized for the entire population and for each treatment group of the lead-in study (the entire groups receiving nalmefene hydrochloride and each treatment group).

For the subjects in the SS and FAS who advance to the run-out period of this trial, the demographic and other baseline characteristics shown in Table 8.1-1, Table 8.1-2, and Table 8.1-3 will be summarized for the entire population and for each treatment group of the run-out period of this trial.

For the SS, important medical history related to alcohol dependence and complications will be summarized by System Organ Class (SOC) and Preferred Term (PT) for the entire population and for each treatment group of the lead-in study.

For the subjects in the SS who advance to the run-out period, important medical history related to alcohol dependence and complications will be tabulated by SOC and PT for the entire population and for each treatment group of the run-out period of this trial.

Table 8.1-1 Demographic and Other Baseline Characteristics

Variables	Method of tabulation	Categories
Age (years old)	Descriptive statistics	-
Age (years old)	Frequency	< 65, 65 ≤
		< 25, 25 ≤ - < 35, 35 ≤ - < 45, 45 ≤ - < 55, 55 ≤ - < 65, 65 ≤
Sex	Frequency	Female, Male
Body weight (kg)	Descriptive statistics	-
	Frequency	< 65, 65 ≤
		< 80, 80 ≤
Height (cm)	Descriptive statistics	-
Body Mass Index (BMI) (kg/m^2) a)	Descriptive statistics	-
	Frequency	< 18.5, 18.5 ≤ - < 25, 25 ≤ - < 30, 30 ≤ - < 40, 40 ≤
		< 25, 25 ≤ - < 30, 30 ≤
Important medical history related to alcohol dependence	Frequency	Yes, No
Complication	Frequency	Yes, No
Smoking history	Frequency	"Now smokes every day," "Now smokes some days (not every day)," "Has smoked," "Never smoked"
Drug abuse history	Frequency	Yes, No
Prior drugs	Frequency	Yes, No
Prior therapies other than BRENDA	Frequency	Yes, No
Concomitant drugs	Frequency	Yes, No
Prior concomitant therapy other than BRENDA	Frequency	Yes, No
CIWA-Ar Total Score (at screening of the lead-in study) b)	Descriptive statistics	-
CIWA-Ar Total Score (at randomization of the lead-in study) b)	Descriptive statistics	-

a) To be calculated using the height at screening and the body weight at the Randomization Visit of the lead-in study.

b) If at least one item is missing, the total score will not be calculated.

Table 8.1-2 Alcohol Drinking History

Variables	Method of tabulation	Categories
Age when started drinking (years old)	Descriptive statistics	-
	Frequency	< 15, 15 ≤ - < 18, 18 ≤
		< 20, 20 ≤
Age when drinking problems detected (years old)	Descriptive statistics	-
	Frequency	< 20, 20 ≤
Family history of problematic alcohol use	Frequency	Yes, No

Table 8.1-3 Treatment History for Drinking Problems

Variables		Method of tabulation	Categories
Age when started treatment for drinking problems (years old)		Descriptive statistics	-
Treatments for alcohol dependence		Frequency	Yes, No
	Inpatient treatment	Frequency	Yes, No
	Inpatient treatment (number of times)	Descriptive statistics	-
	Inpatient treatment, psychiatrist	Frequency	Yes, No
	Inpatient treatment, psychiatrist (number of times)	Descriptive statistics	-
	Inpatient treatment, specialist other than psychiatrist	Frequency	Yes, No
	Inpatient treatment, specialist other than psychiatrist (number of times)	Descriptive statistics	-
	Outpatient treatment	Frequency	Yes, No
	Outpatient treatment (number of times)	Descriptive statistics	-
	Outpatient treatment, psychiatrist	Frequency	Yes, No
	Outpatient treatment, psychiatrist (number of times)	Descriptive statistics	-
	Outpatient therapy, specialist other than psychiatrist	Frequency	Yes, No
	Outpatient treatment, specialist other than psychiatrist (number of times)	Descriptive statistics	-
Treatments for alcohol withdrawal		Frequency	Yes, No
	Inpatient treatment	Frequency	Yes, No
	Inpatient treatment (number of times)	Descriptive statistics	-
	Outpatient treatment	Frequency	Yes, No
	Outpatient treatment (number of times)	Descriptive statistics	-
Treatments for alcohol dependence or withdrawal		Frequency	Yes, No
Participation in Alcoholics Anonymous or other patient groups		Frequency	Never participated, Currently participating, Participated within the past 4 weeks, Participated more than 4 weeks ago

8.2 Implementation Status

8.2.1 Use of Drugs other than Investigational Medicinal Product

For the SS, the number and proportion of subjects who use drugs other than the IMP or "newly initiated therapy for alcohol dependence" will be obtained using the data of the lead-in study and this trial in terms of the "periods and treatment groups" shown in 1), 2), 3). They will be obtained for all drugs by ACT classification (Level 2, Level 3 and Level 4) coded in the WHO Drug Dictionary Enhanced, and by Preferred name.

1) Drugs used during the treatment period of the lead-in study

   For the drugs started by the day prior to Randomization Visit in the lead-in study and continued after the Randomization Visit, or for the drugs started during the treatment period of the lead-in study, the number and the proportion of each will be obtained for each treatment group of the lead-in study (the entire groups receiving nalmefene hydrochloride and each treatment group).

2) Drugs started during the treatment period of this trial

   For the drugs started during the treatment period of this trial, the number and its proportion will be obtained for the entire population and for each treatment group of the lead-in study.

3) Drugs started during the run-out period or the post-treatment observation period of this trial

   For the subjects in the SS who advance to the run-out period of this trial and for the drugs started during the run-out period, or the post-treatment observation period of this trial, the number and the proportion of each will be obtained for the entire population and for each treatment group of the run-out period of this trial.

8.2.2 Status of Non-drug Therapy

For the SS, the number of subjects who newly start a therapy for alcohol dependence and its proportion will be obtained for all non-drug therapies by ACT classification (Level 2, Level 3 and Level 4) coded in the WHO Drug Dictionary Enhanced, and by Preferred name. For prior therapies or concomitant therapies other than BRENDA, or BRENDA approach, tabulation will not be conducted.

9 Safety Analysis

Unless otherwise specified, the following safety analyses will be performed for the SS as the analysis set using data from the lead-in study and this trial

9.1 Extent of Exposure

The study treatment duration will be defined as the study treatment duration (number of days of TLFB during the treatment period) in the lead-in study and the number of TLFB days during the treatment period and the run-out period of this trial.

9.1.1 Duration of Treatment and Duration of Exposure to IMP

The study treatment duration (person-years) and the duration of exposure to the IMP (person-years) in the lead-in study will be obtained for each treatment group of the lead-in study (the entire groups receiving nalmefene hydrochloride and each treatment group). The study treatment duration (person-years) and the duration of exposure to the IMP (person-years) during the treatment period of this trial will be obtained for the entire population and for each treatment group of the lead-in study. In addition, for the subjects who advance to the run-out period of this trial, the study treatment duration (person-years) and the duration of exposure to the IMP (person-years) during the run-out period of this trial will be obtained for each treatment group of the lead-in study and for each treatment group of the run-out period.

9.1.2 Investigational Medicinal Product Compliance

1) Lead-in study and this trial

Descriptive statistics and percentiles (10%, 25%, 75%, 90%) will be obtained for the number of days of IMP administration and the proportion of the number of days of IMP administration to the study treatment duration overall and monthly. Descriptive statistics and percentiles will also be obtained for “the number of days of drinking with IMP administration,” “the number of days of drinking without IMP administration,” “the number of days of not drinking with IMP administration,” “the number of days of not drinking without IMP administration,” and their respective proportions to the number of TLFB days in the study treatment duration. Frequency of days of drinking without IMP administration will also be tabulated. The categories for frequency are 0 day, 1 - 9 days, 10 - 19 days, 20 - 29 days, 30 - 39 days, 40 - 59 days, 60 - 99 days, and ≥100 days. Pooled data from the treatment groups will be used for the tabulation regardless of the treatment groups of the lead-in study or treatment groups of the run-out period of this trial.

For the subjects in the SS who receive nalmefene hydrochloride 20 mg in the lead-in study and the run-out period of this trial, descriptive statistics and percentiles will be obtained for the number of days of IMP administration and the proportion of the number of days of IMP administration to the study treatment duration. Descriptive statistics and percentiles will also be obtained for “the number of days of drinking with IMP administration,” “the number of days of drinking without IMP administration,” “the number of days of not drinking with IMP administration,” “the number of days of not drinking without IMP administration,” and their respective proportions to the number of TLFB days in the study treatment duration. Frequency of days of drinking without IMP administration will also be tabulated. The categories for frequency are 0 day, 1 - 9 days, 10 - 19 days, 20 - 29 days, 30 - 39 days, 40 - 59 days, 60 - 99 days, and ≥100 days.

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

Descriptive statistics and percentiles will be obtained 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 to the study treatment duration for the entire population and for each treatment group of the lead-in study. Descriptive statistics and percentiles will also be obtained for “the number of days of drinking with IMP administration,” “the number of days of drinking without IMP administration,” “the number of days of not drinking with IMP administration,” “the number of days of not drinking without IMP administration,” and their respective proportions to the number of TLFB days in the study treatment duration. Frequency of days of drinking without IMP administration will also be tabulated. The categories for frequency are 0 day, 1 - 9 days, 10 - 19 days, 20 - 29 days, 30 - 39 days, 40 - 59 days, 60 - 99 days, and ≥100 days

3) Treatment period of this trial

Descriptive statistics and percentiles will be obtained 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 to the study treatment duration for the entire population and for each treatment group of the lead-in study. Descriptive statistics and percentiles will also be obtained for “the number of days of drinking with IMP administration,” “the number of days of drinking without IMP administration,” “the number of days of not drinking with IMP administration,” “the number of days of not drinking without IMP administration,” and their respective proportions to the number of TLFB days in the study treatment duration. Frequency of days of drinking without IMP administration will also be tabulated. The categories for frequency are 0 day, 1 - 9 days, 10 - 19 days, 20 - 29 days, 30 - 39 days, 40 - 59 days, 60 - 99 days, and ≥100 days.

4) Run-out period of this trial

For the subjects in the SS who advance to the run-out period, descriptive statistics and percentiles will be obtained 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 to the study treatment duration for each treatment group of the run-out period of this trial. Descriptive statistics and percentiles will also be obtained for “the number of days of drinking with IMP administration,” “the number of days of drinking without IMP administration,” “the number of days of not drinking with IMP administration,” “the number of days of not drinking without IMP administration,” and their respective proportions to the number of TLFB days in the study treatment duration. Frequency of days of drinking without IMP administration will also be tabulated. The categories for frequency are 0 day, 1 - 9 days, 10 - 19 days, and ≥20 days.

Data in which both alcohol consumption and IMP compliance in each study treatment duration are available and neither of them is unknown will be used for tabulation.

9.2 Adverse Events

1) Lead-in study and this trial

Treatment-emergent adverse events (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. 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 of the lead-in study or treatment groups of the run-out period of this trial.

For the subjects in the SS who receive nalmefene hydrochloride 20 mg in the lead-in study and the run-out period of this trial, TEAEs will be summarized for the entire treatment period and for timepoint (lead-in study or this trial) 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. Drug-related TEAEs will be summarized in the same manner.

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

For the subjects in the entire population and in each treatment group of the lead-in study (the entire groups receiving nalmefene hydrochloride and each treatment group), TEAEs will be summarized for the entire treatment period and for timepoint (lead-in study, this trial) 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. TEAEs will also be summarized for the entire treatment period and for timepoint (lead-in study or this trial) by SOC 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. TEAEs that occur in this trial but before the start of the treatment period are included and summarized in the treatment period of this trial.

In addition, TEAEs with an incidence of ≥ 2% in any treatment group of the lead-in study will be summarized for the entire treatment period and for timepoint (lead-in study or this trial).

3) Run-out period of this trial

For the subjects in the SS who advance to the run-out period of this trial, TEAEs will be summarized for each treatment group of the run-out period of this trial 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. TEAEs will also be summarized by SOC 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.

4) Post-treatment observation period of this trial

For the subjects in the SS who advance to the post-treatment observation period of this trial, TEAEs will be summarized for the entire population and for each treatment group of the run-out period of this trial 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. Drug-related TEAEs will be summarized in the same manner.

5) Treatment period with nalmefene hydrochloride

The following summaries will be provided for the entire population and for each treatment group of the lead-in study. For the subjects who receive nalmefene hydrochloride 10 mg or nalmefene hydrochloride 20 mg in the lead-in study, TEAEs occurring in the lead-in study and TEAEs occurring before or during the treatment period of this trial; For the subjects who receive placebo in the lead-in study, TEAEs occurring during the treatment period of this trial after the start of IMP administration; For the subjects who receive nalmefene hydrochloride 20 mg in the run-out period, TEAEs occurring during the run-out period.

For the number of days to the onset of TEAE, the day of initial administration of nalmefene hydrochloride is defined as Day 0. The duration will be from the day of the onset as Day 1 until the day of resolution or confirmation of the outcome.

- TEAEs by time of the first onset after the initial IMP administration
  - The categories of time of the first onset (days) are 0 ≤ - ≤ 84, 85 ≤ - ≤ 168, 169 ≤ - ≤ 252, 253 ≤ - ≤ 336, and 337 ≤. The incidence will be calculated based on the number of subjects who are treated at least 1 day at the relevant timepoint.
  - Median, minimum, and maximum of the time of the first onset (days) will be provided.
- TEAEs by outcome

- If the same event occurs more than once in the same subject, the last confirmed outcome will be used.

- TEAEs by duration
  - The categories of duration (days) are 1 ≤ - ≤ 7, 8 ≤ - ≤ 14, 15 ≤ - ≤ 21, 22 ≤ - ≤ 28, 29 ≤ - ≤ 56, 57 ≤ - ≤ 84, 85 ≤ - ≤ 112, 113 ≤ - ≤ 140, 141 ≤.
  - Median, minimum, and maximum of the duration (days) will be provided.
  - If the same event occurs more than once in the same subject, the longest duration will be used.

Non-serious TEAEs with an incidence of 5% or higher in this trial 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.

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

The following TEAEs will be summarized by SOC and PT as well as "any TEAEs" in terms of the "periods, subjects, treatment groups" shown in 1), 2), 3), 4). The summaries will provide the number of subjects with TEAEs and incidence of those.

- Serious Adverse Event
- Drug-related serious TEAEs

The following TEAEs will be summarized by SOC and PT as well as "any TEAEs" in terms of the "periods, subjects, treatment groups" shown in 1), 2), 3), 4). The summaries will provide the number of subjects with TEAEs and incidence of those. However, for 2), tabulation for timepoint (lead-in study or this trial) will not be performed.

- TEAEs resulting in discontinuation of IMP administration
- Drug-related TEAEs resulting in discontinuation of IMP administration

The following TEAEs will be summarized in terms of the "periods, subjects, treatment groups" shown in 2), 3), 4). The summaries will provide the number of subjects with TEAEs and incidence of those.

- TEAEs leading to death
- Drug-related TEAEs leading to death
- Severe TEAEs
- Drug-related severe TEAEs

1) Lead-in study and this trial
   a) Pooled data from the treatment groups will be used for the tabulation regardless of the treatment groups of the lead-in study or treatment groups in the run-out period of this trial.
   b) Tabulation will be conducted for the subjects in the SS who receive nalmefene hydrochloride 20 mg in the lead-in study and the run-out period of this trial by timepoint (lead-in study or this trial).
2) Lead-in study and the treatment period of this trial

   The TEAEs will be summarized for the entire population and for each treatment group of the lead-in study (the entire groups receiving nalmefene hydrochloride and each treatment group). They will be summarized for timepoint (lead-in study or this trial). TEAEs that occur in this trial but before the start

of the treatment period are included and summarized in the treatment period of this trial.

3) Run-out period of this trial

Tabulation will be performed for the subjects in the SS who advance to the run-out period of this trial for each treatment group of the run-out period of this trial.

4) Post-treatment observation period of this trial

Tabulation will be performed for the subjects in the SS who advance to the post-treatment observation period of this trial for the entire population and for each treatment group of the run-out period of this trial.

By defining the following notable AEs, regarding the TEAEs occurring in the treatment period of the lead-in study and the TEAEs occurring before or during the treatment period of this trial, the number of subjects with TEAEs, the incidence of those, the number of withdrawals, and the percentage of those will be obtained by PT and "any TEAEs" for the entire period and for timepoint (lead-in study or this trial) for the entire population and for each treatment group (the entire groups receiving nalmefene hydrochloride and each treatment group). However, the number of withdrawals and its percentage will be summarized only for this trial.

- Adverse events related to accident or injury
  AEs retrieved from [SMQ] 20000135/Accidents and Injuries
- Adverse events related to convulsion
  AEs retrieved from [SMQ] 20000079/Convulsions
- Adverse events related to depression
  AEs retrieved from [SMQ] 20000167/Depression (excl. suicide and self injury) using narrow search
- Adverse events related to drug abuse
  AEs retrieved from [SMQ] 20000100/Drug abuse, dependence and withdrawal
- Drug-related hepatic disorder
  AEs retrieved from [SMQ] 20000006/Drug related hepatic disorders - comprehensive search
- Alcohol-related hepatic disorder
  AEs retrieved from [SMQ] 20000017/Hepatic disorders specifically reported as alcohol-related
- AEs related to rhabdomyolysis or myopathy
  AEs retrieved from [SMQ] 20000002/Rhabdomyolysis/myopathy
- Psychiatric adverse events
  The following preferred terms will be used.

10010305	Confusional state
10063033	Depressive delusion
10012245	Delusion of replacement
10012244	Delusion of reference
10012241	Delusion of grandeur
10015134	Erotomanic delusion
10023164	Jealous delusion
10041317	Somatic delusion
10034702	Persecutory delusion
10012239	Delusion
10012250	Delusional disorder, grandiose type
10012252	Delusional disorder, mixed type

10012249	Delusional disorder, erotomanic type
10012251	Delusional disorder, jealous type
10012255	Delusional disorder, unspecified type
10012254	Delusional disorder, somatic type
10053195	Delusional disorder, persecutory type
10012258	Delusional perception
10012295	Dementia of the Alzheimer's type, with delusions
10076429	Mixed delusion
10077805	Depersonalisation/derealisation disorder
10012422	Derealisation
10013395	Disorientation
10013457	Dissociation
10062824	Hallucination, synaesthetic
10020928	Hypnopompic hallucination
10019063	Hallucination
10019072	Hallucination, olfactory
10019075	Hallucination, visual
10019070	Hallucination, auditory
10019071	Hallucination, gustatory
10019074	Hallucination, tactile
10062684	Somatic hallucination
10020927	Hypnagogic hallucination
10019079	Hallucinations, mixed
10021403	Illusion
10048294	Mental status changes
10049986	Mental status changes postoperative
10033864	Paranoia
10012355	Dependent personality disorder
10020155	Histrionic personality disorder
10003865	Avoidant personality disorder
10006034	Borderline personality disorder
10029901	Obsessive-compulsive personality disorder
10028712	Narcissistic personality disorder
10034723	Personality disorder of childhood
10034721	Personality disorder
10039651	Schizotypal personality disorder
10039624	Schizoid personality disorder
10002822	Antisocial personality disorder
10033869	Paranoid personality disorder
10040535	Shared psychotic disorder
10061921	Psychotic disorder due to a general medical condition
10061920	Psychotic disorder
10006362	Brief psychotic disorder, with postpartum onset
10048549	Brief psychotic disorder with marked stressors
10056395	Brief psychotic disorder without marked stressors
10043431	Thinking abnormal

- Adverse events related to psychosis or psychotic disorder

  AEs retrieved from [SMQ] 20000117/Psychosis and psychotic disorders using narrow search and AEs defined in the psychiatric adverse events

- Adverse events related to suicide

  AEs retrieved from [SMQ] 20000037/Suicide/self injury

- Nighttime symptoms related to sleep disorder

The following preferred terms will be used.

10022035	Initial insomnia
10022437	Insomnia
10027590	Middle insomnia
10040984	Sleep disorder
10061827	Dyssomnia
10062519	Poor quality sleep
10068932	Terminal insomnia

- Daytime symptoms related to sleep disorder

  The following preferred terms will be used.

10002942	Apathy
10003549	Asthenia
10016256	Fatigue
10020765	Hypersomnia
10024264	Lethargy
10039897	Sedation
10041349	Somnolence

A list of subjects with overdose will be prepared. Overdose is defined by the following preferred terms.

- <PT> 10000381/Accidental overdose
- <PT> 10022523/Intentional overdose

9.4 Subgroup Analyses of Adverse Events

For the following subgroups, regarding the TEAEs occurring in the treatment period of the lead-in study and the TEAEs occurring before or during the treatment period of this trial, the number of subjects with TEAEs and the incidence of those will be obtained by SOC and PT as well as “any TEAEs” for the entire period and for timepoint (lead-in study or this trial) for the entire population and for each treatment group of the lead-in study (the entire groups receiving nalmefene hydrochloride and each treatment group).

- Sex [female, male]
- Age (years old) [< 65, 65 ≤]
- Body Mass Index (BMI) (kg/m^2) [< 25, 25 ≤ - < 30, 30 ≤]

9.5 Clinical Laboratory Tests

For clinical laboratory tests, the following summarization will be performed in terms of the "periods, subjects, treatment groups, baseline, and timepoints" shown in 1), 2), 3).

- Descriptive statistics will be calculated for hematology and chemistry at each timepoint and their changes from baseline.
- Classification (low, normal, and high) based on reference values of hematology and blood chemistry at each timepoint will be summarized in shift tables from baseline.
- Urinalysis at each timepoint will be summarized in shift tables from baseline. Frequency distributions will be prepared for urinary sediment. No summarization will be performed for HCG.

For changes in clinical laboratory values assesses as PCS or related to drug-induced liver injury, the

number and percentage of subjects meeting the criteria (with the number of subjects included in the assessment as a denominator) will be obtained for measured values after baseline in terms of the "periods, subjects, treatment groups, baseline, and timepoints" shown in 1), 2), 3). However, data at each timepoint will not be tabulated. For condition 1), data will be summarized for the lead-in study and this trial as a whole. For condition 2), data will be summarized for timepoint (lead-in study or this trial) in addition to the lead-in study and the treatment period of this trial as a whole. For condition 3), data will be summarized for the run-out period and for the post-treatment observation period. The subjects who meet the criteria for changes in clinical laboratory values assessed as PCS or related to drug-induced liver injury will be tabulated in their respective tables. The criteria for PCS values are shown in Appendix 15.1, and the criteria for changes in clinical laboratory values related to drug-induced hepatic disorder are shown below. For changes in clinical laboratory values related to drug-induced liver injury, when subjects meet any of the following criteria, they will be tabulated as change in clinical laboratory values related to drug-induced liver injury and tabulated by individual assessment criteria.

- AST or ALT ≥ 3 times the upper limit of normal
- AST or ALT ≥ 5 times the upper limit of normal
- AST or ALT ≥ 10 times the upper limit of normal
- AST or ALT ≥ 20 times the upper limit of normal
- Total bilirubin ≥ 2 times the upper limit of normal
- Alkaline phosphatase ≥ 1.5 times the upper limit of normal
- AST or ALT ≥ 3 times the upper limit of normal and total bilirubin ≥ 2 times the upper limit of normal
- AST or ALT ≥ 3 times the upper limit of normal and total bilirubin ≥ 2 times the upper limit of normal, and an alkaline phosphatase ≤ 1.5 times the upper limit of normal
- AST or ALT ≥ 3 times the upper limit of normal, total bilirubin ≥ 2 times the upper limit of normal or INR/prothrombin time ≥ 1.5 times the upper limit of normal, and alkaline phosphatase ≤ 1.5 times the upper limit of normal

Classification (low, normal, and high) based on the PCS criteria of hematology, blood chemistry, and prolactin will be summarized in shift tables from baseline in terms of the "periods, subjects, treatment groups, baseline, and timepoints" shown in 1), 2), 3). However, data at each timepoint will not be tabulated. For condition 1), data will be summarized for the lead-in study and this trial as a whole. For condition 2), data will be summarized for timepoint (lead-in study or this trial) in addition to the lead-in study and the treatment period of this trial as a whole. For condition 3), data will be summarized only for the run-out period.

1) Lead-in study and this trial
   a) The data in the SS will be summarized with baseline of the lead-in study. The timepoints are baseline, Weeks 12 and 24 of the lead-in study, and Week 12, Week 24, Week 28 (the run-out period), Week 32 (the post-treatment observation period) and the final evaluation point of this trial. Pooled data from the treatment groups will be used for the tabulation regardless of the treatment groups of the lead-in study or treatment groups in the run-out period of this trial.
   b) Tabulation will be conducted for the subjects in the SS who receive nalmefene hydrochloride 20 mg in the lead-in study group and the run-out period of this trial. Baseline and timepoints are the

same as in a).

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

The data in the SS will be summarized with baseline of the lead-in study. The timepoints are baseline, Weeks 12 and 24 of the lead-in study, Weeks 12 and 24, and the final evaluation of the treatment period of this trial. The data will be summarized for the entire population and for each treatment group of the lead-in study (the entire groups receiving nalmefene hydrochloride and each treatment group).

3) The run-out period and the post-treatment observation period of this trial

The data of the subjects in the SS who advance to the run-out period of this trial will be summarized with baseline II (baseline of the run-out period and the post-treatment observation period). The timepoints are baseline II, Week 28 (the run-out period), Week 32 (the post-treatment observation period) and the final evaluation after the run-out period of this trial. Data will be summarized for the entire population and for each treatment group of the run-out period of this trial.

In addition, a scatter plot will be prepared for hematology and blood chemistry with the data at the baseline of the lead-in study (X-axis) and the final evaluation of the treatment period (Y-axis).

9.6 Vital Signs

The following data will be tabulated in terms of the same "period, subjects, treatment groups, baseline, and timepoints" as for clinical laboratory tests. However, for the timepoints of the treatment period, the timepoints of tests planned in the protocol will also be included in the tabulation.

- Descriptive statistics will be calculated for systolic and diastolic blood pressures, pulse rate, and body weight at each timepoint and their changes from baseline.

For PCS, frequency will be summarized and listed in the same manner as for clinical laboratory tests. The criteria for PCS are shown in Appendix 15.2.

9.7 Twelve-lead Electrocardiogram (results obtained from the central ECG laboratory)

The following data will be tabulated in terms of the same "period, subjects, treatment groups, baseline, and timepoints" as for clinical laboratory tests.

- Descriptive statistics will be calculated for heart rate, RR interval, PR interval, QRS interval, QT interval, QTcB, and QTcF at each timepoint, and their changes from baseline.
- A shift table of “Abnormal Significant,” “Abnormal Insignificant,” or “Normal” at each timepoint from baseline will be provided.
- QTcB/QTcF at each timepoint and their changes from baseline will be categorically summarized for frequency. The categories of QTcB and QTcF frequency summary are > 450 msec, > 480 msec, and > 500 msec, and the categories of QTcB and QTcF change frequency summary are > 30 msec and > 60 msec. For the worst values, frequency tabulation will be performed using the same categories. For the worst values for 1) Lead-in study and this trial, the worst values in the lead-in study and this trial as a whole will be used. For 2) Lead-in study and the treatment period of this trial, the worst values in each timepoint (the lead-in study and this trial) in addition to the worst

values in the lead-in study and the treatment period of this study as a whole will be used. For 3) The run-out period and the post-treatment observation period of this trial, the worst values pooled from the run-out period and the post-treatment observation period will be used.

For PCS, frequency will be summarized and listed in the same manner as for clinical laboratory tests. The criteria for PCS are shown in Appendix 15.3.

In addition, in the same manner as for the clinical laboratory test, classification (low, normal, and high) shift tables for categorical values based on PCS criteria for RR intervals, PR intervals, QRS intervals, and QT intervals versus baseline will be provided.

9.8 Physical Examination

The physical examinations ("Abnormal Significant," "Abnormal Insignificant," and "Normal") will be categorically summarized for frequency at each timepoint in terms of the "periods, subjects, treatment groups, and timepoints" shown in 1), 2), 3).

1) Lead-in study and this trial
   a) Tabulation will be conducted for the SS. The timepoints are screening, Weeks 12 and 24 of the lead-in study, and Weeks 12, 24, 28 (the run-out period), 32 (the post-treatment observation period), and the final evaluation point of this trial. Pooled data from the treatment groups will be used for the tabulation regardless of the treatment groups of the lead-in study or treatment groups in the run-out period of this trial.
   b) Tabulation will be conducted for the subjects in the SS who receive nalmefene hydrochloride 20 mg in the lead-in study group and the run-out period of this trial. The timepoints are the same as in a).
2) Lead-in study and the treatment period of this trial
   Tabulation will be conducted for the SS. The timepoints are screening, Weeks 12 and 24 of the lead-in study, Weeks 12 and 24, and the final evaluation of the treatment period of this trial. The data will be summarized for the entire population and for each treatment group of the lead-in study (the entire groups receiving nalmefene hydrochloride and each treatment group).
3) The run-out period and the post-treatment observation period of this trial
   Tabulation will be conducted for the subjects in the SS who advance to the run-out period of this trial. The timepoints are Week 24, Week 28 (the run-out period), Week 32 (the post-treatment observation period) and the final evaluation after the run-out period of this trial. Data will be summarized for the entire population and for each treatment group of the run-out period of this trial.

9.9 POMS

The following data will be tabulated in terms of the same "period, subjects, treatment groups, baseline, and timepoints" as for clinical laboratory tests.

- Descriptive statistics will be provided for total mood disturbance (TMD) score and each factor (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment) at each timepoint and their changes from baseline.

For changes in the TMD score from baseline of the lead-in study and the treatment period of this trial, MMRM analysis will be performed in the same manner as for the number of HDDs. The timepoints are Weeks 12 and 24 of the lead-in study and Weeks 12 and 24 of this trial.

9.10 C-SSRS

The following data will be tabulated in terms of the same "period, subjects, treatment groups, baseline, and timepoints" as for clinical laboratory tests. However, for the timepoints of the treatment period, the timepoints of tests planned in the protocol will also be included in the tabulation. Baseline of the treatment period will be the Randomization Visit (Visit 2) of the lead-in study, and baseline II of the run-out period and post-treatment observation period will be Week 24 of this trial (Visit 10).

- The frequency of Categories 1-10 shown below will be tabulated at each timepoint and any time after baseline. For 1) Lead-in study and this trial, "any time after baseline" is defined as any time after baseline of the lead-in study and this trial as a whole. For 2) Lead-in study and the treatment period of this trial, tabulation will be conducted at any time after baseline of the lead-in study and this trial as a whole as well as any time after baseline of each timepoint (lead-in study or this trial). For 3) The run-out period and the post-treatment observation period of this trial, tabulation will be conducted at any time with pooled data from the run-out period and the post-treatment observation period.
  - 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
- Frequency of the following C-SSRS item will be tabulated at each timepoint and any time after baseline. Definition of "Any time after baseline" will be the same as in the frequency tabulation for Categories 1-10 above.
  - Self-injurious behavior without suicidal intent
- The following variables will be derived using the above Categories 1-10. These variables will also be summarized in a frequency table. For 1) Lead-in study and this trial, tabulation will be conducted for the lead-in study and this trial as a whole. For 2) Lead-in study and the treatment period of this trial, tabulation will be conducted for the lead-in study and this trial as a whole as well as for each timepoint (lead-in study or this trial). For 3) The run-out period and the post-treatment observation period of this trial, tabulation will be conducted separately for the run-out period and for the post-treatment observation period.
  - Suicidal ideation (1-5)
    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 (6-10)
    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 (1-10)
  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[c] 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 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 any time at screening or pre-baseline in the lead-in study.

- Maximum Suicidal ideation score at post-baseline visits will be summarized in shift tables from Suicidal ideation score at baseline. For 1) Lead-in study and this trial, tabulation will be conducted for the lead-in study and this trial as a whole. For 2) Lead-in study and the treatment period of this trial, tabulation will be conducted for the lead-in study and the treatment period of this trial as a whole as well as for each timepoint (lead-in study or this trial). For 3) The run-out period and the post-treatment observation period of this trial, tabulation will be conducted separately for the run-out period and for the post-treatment observation period.
- The following C-SSRS categories will be derived and they will be summarized in shift tables from baseline at each timepoint after baseline.
  - C-SSRS Category
    "No suicidal ideation or behavior,” "Suicidal ideation,” "Suicidal behavior"
    In a case of both "Suicidal ideation" and "Suicidal behavior,” it is included in "Suicidal behavior.”

9.11 Dependence Survey

Answers to each question of dependence survey A at the end of the run-out period and their overall score, and answers to each questions of dependence survey B at the end of the post-treatment observation period and their overall score will be summarized as frequency for the treatment group of the run-out period of this trial. For the overall score, the worst value in each survey will be used.

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[c] 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

10 Efficacy Analysis

Unless otherwise specified, the following efficacy analyses will be performed for the FAS as the analysis set using data from the lead-in study and this trial.

10.1 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 changes from baseline for each treatment group of the lead-in study (nalmefene hydrochloride 10 mg, nalmefene hydrochloride 20 mg, and placebo groups). The time course of the change from baseline (mean ± standard deviation) will be plotted for each treatment group.

For the subjects in the FAS who advance to the run-out period of this trial, the number of HDDs in the run-out period of this trial and changes from baseline II will be summarized with descriptive statistics for each treatment group of the run-out period of this trial.

As an exploratory analysis, MMRM analysis will be performed for changes in the number of HDDs from baseline at each timepoint of the lead-in study and the treatment period of this trial, and the time course of the change from baseline (least squares mean ± standard error) will be plotted. The baseline will be the one in the lead-in study. The model includes 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, for the subjects in the FAS who advance to the run-out period of this trial, changes in the number of HDDs from baseline II of the run-out period of this trial will be analyzed by using an analysis of covariance (ANCOVA) model with treatment group of the run-out period of this trial and sex as fixed, categorical effect and the number of HDDs at baseline II as covariance.

In addition, the number of HDDs at each timepoint of the lead-in study and the treatment period of this trial and changes from baseline will be summarized with descriptive statistics for each treatment group of the lead-in study with another grouping (the entire groups receiving nalmefene hydrochloride and placebo group) and their time course (mean ± standard deviation) will be plotted. MMRM analysis and the time-course plot (least squares mean ± standard error) will also be prepared.

10.2 TAC

Total alcohol consumption will be summarized with descriptive statistics, and the time-course plot (mean ± standard deviation) will be prepared in the same manner as with the number of HDDs. The MMRM analysis, the time-course plot (least squares mean ± standard error) and ANCOVA analysis will be performed in an exploratory manner. As with the number of HDDs, TAC will be summarized with descriptive statistics for each treatment group of the lead-in study with another grouping (the entire groups receiving nalmefene hydrochloride and placebo group), and their time course (mean ± standard deviation) will be plotted. MMRM analysis and the time-course plot (least squares mean ± standard error) will also be prepared.

10.3 RSDRL

Frequency of RSDRL at each timepoint of the lead-in study and the treatment period of this trial will be summarized for each treatment group (nalmefene hydrochloride 10 mg, nalmefene hydrochloride 20 mg, and placebo) of the lead-in study.

Observed case data will be analyzed without imputation of missing values. Furthermore, analyses will be performed for the entire FAS, where missing values will be handled as non-responders.

10.4 RLDRL

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

10.5 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.

10.6 Heavy Drinking Day Responder Rate

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

10.7 CGI-S

In the same manner as the number of HDDs, CGI-S will be summarized with descriptive statistics, and exploratory MMRM analysis will be performed. The timepoints of the lead-in study and the treatment period of this trial are Weeks 1, 2, 4, 8, 12, 16, 20, and 24 of the lead-in study and Weeks 0, 1, 2, 4, 8, 12, 16, 20, and 24 of this trial. The number and proportion of subjects with each score at each timepoint will be obtained. However, if the assessment is "0. Not assessed," the data will be handled as missing, and the proportion will be calculated excluding the subjects with the assessment of "0. Not assessed." In addition, descriptive statistics will be calculated for the subgroup excluding the subject with the baseline assessment of "1. Normal, not at all ill" and the subgroup of the subjects with the baseline assessment of "1. Normal, not at all ill," and MMRM analysis will be performed.

10.8 CGI-I

In the same manner as with the number of HDDs, CGI-I will be summarized with descriptive statistics, and exploratory MMRM analysis will be performed. The timepoints of the lead-in study and the treatment period of this trial are Weeks 1, 2, 4, 8, 12, 16, 20, and 24 of the lead-in study and Weeks 0, 1, 2, 4, 8, 12, 16, 20, and 24 of this trial. However, the scores at each timepoint will be analyzed, as opposed to changes from baseline, since the score itself is an assessment of change from baseline. The CGI-S at baseline will be included for covariate adjustment. The number and proportion of subjects with each score at each timepoint will be obtained. However, if the assessment is "0. Not assessed," the data will be handled as

missing, and the proportion will be calculated excluding the subjects with the assessment of "0. Not assessed."

10.9 SF-36

For the 8 subscales of SF-36 (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, descriptive statistics will be calculated in the same manner as with the number of HDDs, and MMRM analysis will be performed in an exploratory manner. The timepoints of the lead-in study and the treatment period of this trial are Weeks 12 and 24 of the lead-in study, and Weeks 12 and 24 of this trial.

10.10 EQ-5D-3L

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

10.11 AQoLS

In the same manner as with the number of HDDs, AQoLS total score will be summarized with descriptive statistics, and exploratory MMRM analysis will be performed.

10.12 RUMQ-ADP

Frequency will be calculated for each of the following items in sociodemographic, resource consumption, and sick leaves at each timepoint of the lead-in study and the treatment period of this trial (baseline, Weeks 12 and 24 of the lead-in study, and Weeks 12 and 24 of this trial) for each treatment group of the lead-in study (nalmefene hydrochloride 10 mg, nalmefene hydrochloride 20 mg, and placebo).

For the subjects in the FAS who advance to the run-out period of this trial, frequencies of the same items will be calculated for each treatment group of the run-out period of this trial.

- Sociodemographic
  - Marital status [single, married/living together, divorced/separated, widowed]
  - Number of children per household [0, 1, 2, 3, 4 ≤]
  - Residence [countryside, urban area]
- Resource consumption
  - Use of at least one healthcare resource [yes, no]
  - Number of consultations with general physicians [0, 1, 2, 3, 4, 5, 6 ≤]
  - Number of consultations with psychiatrists [0, 1, 2, 3, 4, 5, 6 ≤]
  - Number of consultations with other specialists [0, 1, 2, 3, 4, 5, 6 ≤]
  - Number of consultations with psychologists [0, 1, 2, 3 ≤]
  - Number of consultations with nurses [0, 1, 2, 3 ≤]

  - Number of consultations with social workers [0, 1, 2, 3 ≤]
  - Number of consultations with self-help groups (Alcoholics Anonymous, etc.) [0, 1, 2, 3 ≤]
  - Psychiatric hospitalization [yes, no]
  - Emergency admission [yes, no]
  - General hospitalization [yes, no]
  - Hospitalization for surgery [yes, no]
  - Other (other than psychiatry, emergency care, general practice, surgery) hospitalization [yes, no]
- Sick leaves
  - Sick leaves [yes, no]

10.13 Gamma-glutamyl Transferase

GGT at each timepoint in the lead-in study and the treatment period of this trial (baseline, Weeks 12 and 24 of the lead-in study, and Weeks 12 and 24 of this trial) will be summarized with descriptive statistics and geometric mean for each treatment group of the lead-in study.

For log-transformed GGT, exploratory MMRM analysis will be performed in the same manner as the number of HDDs. The least squares mean for each treatment group at each timepoint will be estimated, and the estimate results will be inversely log-transformed to obtain the mean on the actual scale. 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. The timepoints are Weeks 12 and 24 of the lead-in study and Weeks 12 and 24 of this trial.

10.14 ALT

For ALT, descriptive statistics and geometric mean will be obtained in the same manner as the analysis of GGT.

For log-transformed ALT, MMRM analysis will be performed in the same manner as the analysis of GGT.

11 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 the subjects is approximately 400.

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

12 Changes from the Analysis Method Planned in the Protocol

Changes from the analysis method planned in the protocol are described below.

- Change in AQoLS endpoint from "each domain and item" to "total score"
  Reason: Revised based on Validation of a new patient-reported outcome instrument of health-related quality of life specific to patients with alcohol use disorder: the Alcohol Quality of Life Scale (AQoLS) (2015)[3].

- Deletion of frequency summary of RSDRL, RLDRL, TAC 70% response rate, and HDD response rate for the subjects advancing to the run-out period
  Reason: In the run-out period, rebound phenomena will be checked regarding the amount of alcohol consumption. However, since these endpoints evaluate decrease in alcohol consumption but cannot evaluate rebound phenomena, they were deleted.

- Deletion of descriptive statistics for log-transformed GGT and ALT
  Reason: For log-transformed GGT and ALT, MMRM analysis will be conducted in an exploratory manner. The least squares mean for each treatment group at each timepoint will be estimated, and the mean on the actual scale will be calculated by inversely log-converting the estimated results.

13 References

1 Shunichi Fukuhara, Yoshimi Suzukamo. Manual of SF-36v2 Japanese version: Institute for Health Outcomes and Process Evaluation Research; Kyoto, 2004.

2 Tsuchiya A, Ikeda S, Ikegami N, et al. Estimating an EQ-5D population value set: The case of Japan. Health Economics 2002; 11(4):341-353.

3 A. Luquiens, et al. Validation of a new patient-reported outcome instrument of health-related quality of life specific to patients with alcohol use disorder: the Alcohol Quality of Life Scale (AQoLS) Quality of Life Research 2015

14 Revision History

Not applicable as this is the first version.

Version No.	Revision date	Item Number/ Item Name	Before revision	After revision	Reason for revision

15 APPENDIX

15.1 PCS Criteria for Clinical Laboratory Tests

Items with low and high criteria will be analyzed separately for low and high values.

Variables	Criteria
Hematology	
Red blood cell count	< 3,000,000/ mm^3
Hematocrit Female	≤ 32 %
Hematocrit Male	≤ 37 %
Hemoglobin Female	≥ 16.5 g/dL
	≤ 9.5 g/dL
Hemoglobin Male	≥ 18.5 g/dL
	≤ 11.5 g/dL
MCV	≥ 1.2 × upper limit of normal
	≤ 0.8 × lower limit of normal
Total white blood cell count	≥ 16,000/uL
	< 2,800/uL
Neutrophils	≥ 85 %
	≤ 20 %
Eosinophils	≥ 10 %
Basophils	≥ 10 %
Lymphocytes	≥ 75 %
	≤ 10 %
Monocytes	≥ 15 %
Platelet count	≥ 700,000/mm^3
	≤ 75,000/mm^3
Blood chemistry	
Total bilirubin	≥ 2 × upper limit of normal
Alkaline phosphatase	≥ 3 × upper limit of normal
ALT	≥ 3 × upper limit of normal
AST	≥ 3 × upper limit of normal
Gamma-glutamyl Transferase	≥ 200 U/L
INR/prothrombin time	≥ 2.0
Albumin	≤ 2.7 g/dL
Cholinesterase	No reference range
Total cholesterol	≥ 302 mg/dL
Triglycerides	≥ 500 mg/dL
Creatinine	≥ 1.5 × upper limit of normal
	≤ 0.5 × lower limit of normal
BUN	> 30 mg/dL
Sodium	≥ 155 mEq/L
	≤ 125 mEq/L
Potassium	≥ 6.0 mEq/L
	≤ 3.0 mEq/L
Bicarbonate (HCO3-)	≥ 38 mmol/L
	≤ 12 mmol/L
Calcium	≥ 12.0 mg/dL
	≤ 7.2 mg/dL
Glucose	≥ 162 mg/dL
	≤ 63 mg/dL
CRP	No reference range
Urinalysis	

Protein	Increase ≥ 2 levels from baseline
Glucose	Increase ≥ 2 levels from baseline
Occult blood	Increase ≥ 2 levels from baseline
Ketones	Increase ≥ 2 levels from baseline
Urinary sediment	No reference range
Others	
Prolactin	≥ 67.5 ug/L

15.2 PCS Criteria for Vital Signs

Analyses will be performed separately for increase and decrease.

Variables	Criteria
Systolic blood pressure	≥ 180 mmHg and change from baseline ≥ 20 mmHg
	≤ 90 mmHg and change from baseline ≤ -20 mmHg
Diastolic blood pressure	≥ 105 mmHg and change from baseline ≥ 15 mmHg
	≤ 50 mmHg and change from baseline ≤ -15 mmHg
Pulse rate	≥ 120 bpm and change from baseline ≥ 15 bpm
	≤ 50 bpm and change from baseline ≤ -15 bpm
Body weight	Change from baseline ≥ 7%
	Change from baseline ≤ -7%

15.3 PCS Criteria for 12-lead ECG

Analyses will be performed separately for increase and decrease.

Variables	Criteria
Heart rate	≥ 120 bpm and change from baseline ≥ 15 bpm
	≤ 50 bpm and change from baseline ≤ -15 bpm
RR interval	≥ 1200 msec
	< 500 msec
PR interval	≥ 260 msec
QRS interval	≥ 150 msec
QT interval	≥ 500 msec
QTcB	≥ 500 msec or change from baseline ≥ 60 msec
QTcF	≥ 500 msec or change from baseline ≥ 60 msec