


Long-term safety and efficacy of nalmefene in Japanese patients with alcohol dependence

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Aim: The safety and efficacy of nalmefene in Japanese patients with high or very high World Health Organization drinking risk level of alcohol dependence were assessed in a multicenter, randomized, double-blind, placebo-controlled, phase 3 (lead-in) study. Here, the long-term safety and efficacy of nalmefene in an open-label extension of the lead-in study are presented.

Methods: Patients who completed the 24-week lead-in study were eligible for the extension study, where they were treated with nalmefene 20 mg as needed for 24 weeks. The long-term safety and efficacy of nalmefene 20 mg during the total 48-week period were evaluated. Treatment-emergent adverse events during the study period were recorded and change from baseline in the number of heavy drinking days and total alcohol consumption were calculated.

Results: Overall, long-term nalmefene 20 mg was well tolerated; the main treatment-emergent adverse events reported

in $\geq 5\%$ of patients included nasopharyngitis (37.2%), nausea (36.5%), somnolence (21.2%), dizziness (16.8%), malaise (14.6%), and vomiting (12.4%). The number of heavy drinking days and total alcohol consumption decreased from baseline to 48 weeks (mixed model for repeated measures, least squares mean \pm standard error, -15.09 ± 0.77 days/month and -53.20 ± 2.29 g/day, respectively) during the study.

Conclusion: This long-term evaluation in Japanese patients with high or very high drinking risk levels of alcohol dependence indicated that nalmefene was safe, well tolerated, and efficacious.

Keywords: alcohol dependence, drinking behavior, drug therapy, opioid, safety.

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Alcohol dependence is a major health problem worldwide, and high alcohol consumption is associated with more than 200 diseases and injury conditions.¹ Reportedly, 5.9% of all deaths and 5.1% of the global burden of diseases and injuries are attributable to alcohol consumption.¹ An epidemiological survey conducted in Japan estimated that around 1.07 million individuals had a lifetime experience of alcohol dependence, of whom only 13.6% were receiving treatment.²

Until recently, abstinence was regarded as a major goal for the treatment of alcohol dependence. However, approximately half of patients who seek medical treatment for alcohol dependence prefer reduction in alcohol consumption over complete abstinence as a treatment option.³ The American Psychiatric Association and the European Medicines Agency have considered reduction in alcohol consumption as one of the strategies for the treatment of patients with alcohol dependence.^{4,5} The Japanese guidelines for the treatment of alcohol dependence consider reduction in alcohol consumption as an appropriate treatment goal as well; however, abstinence is still set as the primary goal.⁶

Nalmefene is an opioid antagonist of the μ and δ receptors and a partial agonist of the κ receptor.^{7,8} It has been approved in the European Union, Japan, and several other countries for reducing alcohol consumption in patients with alcohol dependence who have high or very high drinking risk level (DRL). Previous studies have demonstrated the efficacy and safety of nalmefene in Caucasian patients with alcohol dependence.^{9–11}

In the previous long-term study in Caucasian patients, the subgroup analysis demonstrated that nalmefene treatment was more effective in patients with a high or very high DRL as the target population compared with the full analysis population of patients with a medium to very high DRL.¹² A multicenter, randomized, double-blind, placebo-controlled, phase 3 study that investigated the efficacy of nalmefene in Japanese patients with a high or very high DRL of alcohol dependence reported a significant reduction in the number of heavy drinking days (HDD) and total alcohol consumption (TAC) with 24-week treatment.¹³ By extending this phase 3 (lead-in) study,

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The results from this study were presented at the 19th Congress of the International Society for Biomedical Research on Alcoholism (ISBRA) held in Kyoto, Japan in September 2018.

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the long-term safety and efficacy of nalmefene 20 mg were evaluated with a prospective, open-label study.

Methods

Study design and patients

The lead-in study was conducted from 9 February 2015 to 30 July 2016 and the extension study was conducted from 13 July 2015 to 18 January 2017 at 80 sites in Japan. The details of the lead-in study have been previously reported (ClinicalTrials.gov identifier: NCT02364947).¹³ The study consisted of a 2-week screening period, followed by a 24-week treatment period (nalmefene hydrochloride 20 mg, 10 mg, or matched placebo). All patients who completed the lead-in study were eligible for the extension study and those who provided a written informed consent were included (ClinicalTrials.gov NCT02382276). The inclusion and exclusion criteria for enrollment in the extension study were the same as in the lead-in study.¹³

The extension study consisted of a 24-week open-label, uncontrolled treatment period when all patients received nalmefene 20 mg as needed, followed by a 4-week double-blind, placebo-controlled run-out period when patients were randomized 1:1 to receive nalmefene 20 mg or placebo, and a 4-week post-treatment follow-up period (Fig. S1). The total treatment period with nalmefene 20 mg was 48 weeks (combined 48 weeks comprised of 24 weeks in the lead-in study and 24 weeks in the extension study). Patients were instructed to take one tablet orally on days they perceived themselves at risk of drinking alcohol, preferably 1–2 h before the anticipated time of drinking or as soon as drinking started. Maximum permitted frequency of administration was one tablet per day; the use of divided doses was not permitted.

The run-out period was planned to assess the effect of nalmefene discontinuation and possible dependence due to nalmefene after 24 weeks of treatment, and the follow-up period was designed to evaluate the safety and withdrawal symptoms. All patients included in the extension study participated in a psychosocial support program with the BRENDA model that aimed to help in changing behavior and enhancing adherence to treatment.^{4,14,15}

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Council for Harmonization's harmonized tripartite guideline for good clinical practice. The study protocol was approved by the institutional review board at each participating center.

Outcome measures

Safety assessments involved recording treatment-emergent adverse events (TEAE), clinical laboratory values, vital signs, bodyweight, 12-lead electrocardiogram, Columbia Suicide Severity Rating Scale (C-SSRS), and a survey on dependence due to nalmefene. The TEAE were summarized using MedDRA/J Version 19.0 (MedDRA Japanese Maintenance Organization, Tokyo, Japan). The dependence survey was conducted at the end of the run-out period using the Dependence Assessment Form (Dependency 2-A) and withdrawal symptoms were assessed at the end of the follow-up period using the Withdrawal Assessment Form (Dependency 2-B).¹⁶ Details of these forms are provided in Appendix S1 (Study Assessments file). The mean administration rate of nalmefene 20 mg throughout the 48-week treatment period was calculated. The administration rate of nalmefene 20 mg according to the presence or absence of TEAE was also calculated.

The efficacy analysis included change from baseline in the number of HDD and TAC. The number of HDD was defined as the number of days per month (28 consecutive days) with alcohol consumption of >60 g/day for men and >40 g/day for women. TAC was defined as the average daily alcohol consumption in g/day. The Timeline Followback Method was used to obtain estimates of daily intake of nalmefene and alcohol consumption.¹⁷

Other efficacy assessments included: the proportion of patients with a downward shift in DRL of ≥ 2 categories (response shift DRL [RSDRL]); the proportion of patients with low or lower DRL

(response low DRL [RLDRL]); the proportion of patients with a 70% decrease in TAC (TAC70); the proportion of patients with ≤ 4 HDD (HDD response); Clinical Global Impression – Severity of Illness (CGI-S) score; Clinical Global Impression – Global Improvement (CGI-I) score; 36-item Short-Form Health Survey (SF-36) score; EuroQol 5 Dimension (EQ-5D) score; Alcohol Quality of Life Scale (AQoLS) score (Japanese version); and serum γ -glutamyltransferase (GGT) and alanine aminotransferase (ALT) levels. The treatment completion rate (i.e., the proportion of patients who completed the treatment with nalmefene 20 mg during the study) was also calculated.

Statistical analysis

The safety analysis set (SS) included all patients who received at least one dose of study medication during the 24-week treatment period in the extension study. Full analysis set (FAS) included all patients from the SS who had data available for HDD at baseline in the lead-in study and at one or more time points in the extension study.

Descriptive statistics were used to describe the number of dosing days with nalmefene and the dose of nalmefene used during the study. Efficacy data were summarized using descriptive statistics in the FAS. Data for the nalmefene 20 mg and placebo groups were evaluated using the mixed model for repeated measures (MMRM) analysis of the FAS (nalmefene 20 mg, 10 mg, and placebo), and the estimate for nalmefene 20 mg was provided in line with the main purpose of this study, which was to evaluate the long-term efficacy of nalmefene 20 mg. The primary efficacy analysis was based on comparisons with baseline, but supplementary comparisons with placebo were included as a reference for some end-points. Baseline data from the lead-in study were used to calculate the rate of reduction in HDD and TAC at the end of the 24-week treatment period in the extension study. Baseline for the run-out period and the follow-up period was Week 24 of the treatment period in the extension study. MMRM was used to analyze the change from baseline in HDD and TAC with a fixed effect of treatment, sex, time point, treatment-by-time-point interaction, baseline value, and baseline value-by-time-point interaction. CGI-S, CGI-I, SF-36, EQ5D, AQoLS, GGT, and ALT were also evaluated using MMRM analysis. HDD and TAC during the run-out period were analyzed using the analysis of covariance. SAS Version 9.4 (SAS Institute, Tokyo, Japan) was used for statistical calculations.

Using post-hoc analysis, we calculated the mean change of HDD and TAC with their 95% confidence intervals (CI). For the treatment period, the changes were from baseline to Week 48 for nalmefene 20 mg and from Week 24 to Week 48 for the placebo group. For the run-out period, the changes were from baseline to Week 4 for both the nalmefene 20 mg and placebo groups. For the RSDRL, RLDRL, TAC70, and HDD response, the 95%CI of the percentages were calculated in the nalmefene 20 mg and placebo groups at Week 24 or Week 48.

In addition, the administration rate of nalmefene 20 mg according to the presence or absence of TEAE was calculated.

Results

Patients

Of the 547 patients who completed the lead-in study, 405 patients entered the extension study (Fig. 1). Two patients in the nalmefene 20 mg group did not receive the study treatment. Of the remaining 403 patients, 137, 94, and 172 patients had received nalmefene 20 mg, 10 mg, and placebo in the lead-in study, respectively.

A total of 403 patients were included in the SS, while the FAS included 400 patients. The baseline characteristics and demographics of patients who received nalmefene 20 mg in the lead-in study were similar to those of the overall patient population of the extension study (Table 1).

In the patients treated with nalmefene 20 mg throughout the 48-week treatment period ($n = 137$), the treatment completion rate for nalmefene 20 mg was 92%. In these patients, the mean administration

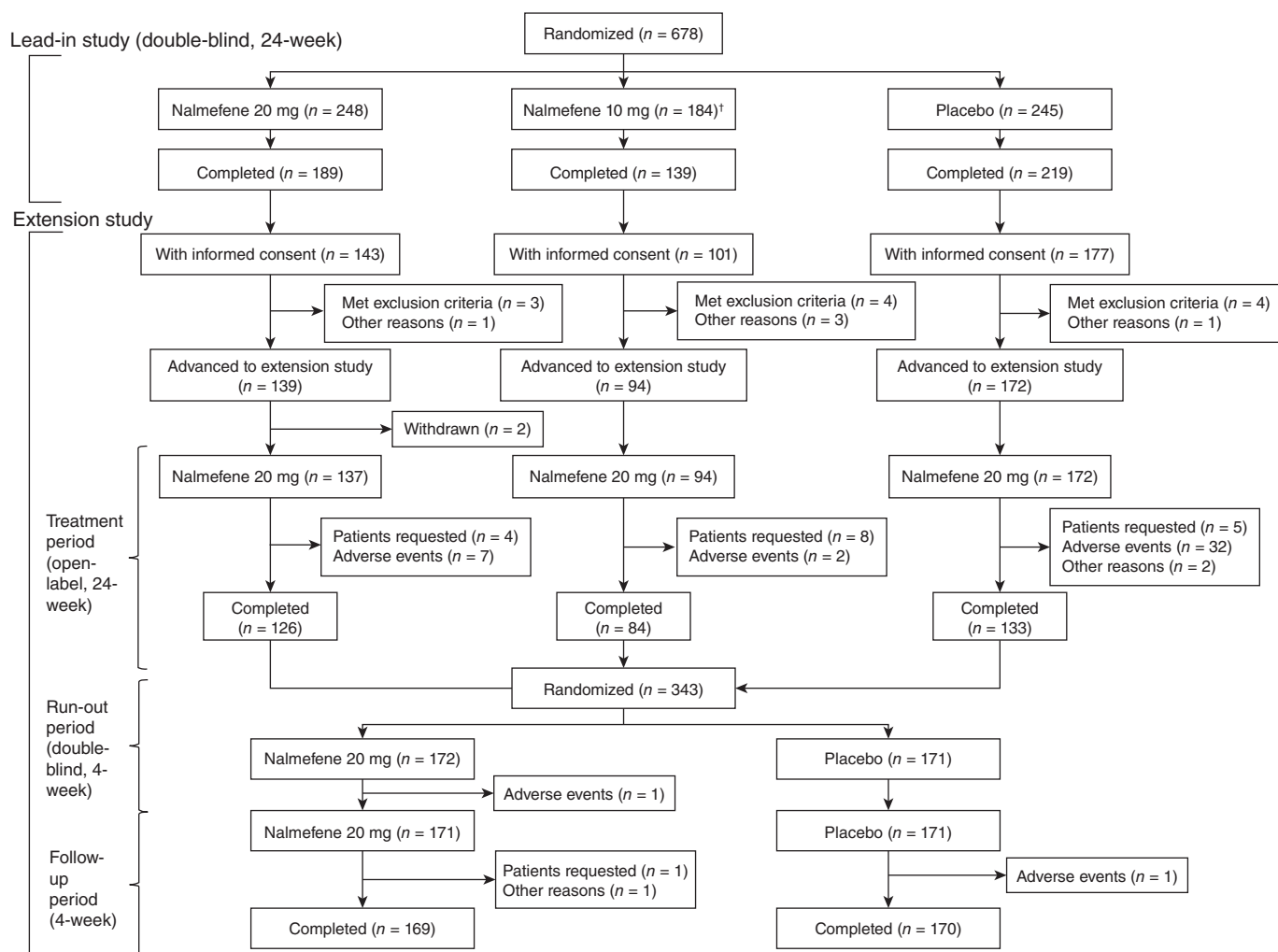


Fig. 1 Patient flow. Of the 403 patients, 137, 94, and 172 patients had received nalmefene 20 mg, 10 mg, and placebo, respectively, and were included in the safety analysis set. After exclusion of three patients who did not have the data for the number of heavy drinking days at baseline or first dosing in the placebo, a total of 400 patients were included in the full analysis set. *In the lead-in study, 185 patients were randomly assigned to nalmefene 10 mg and one patient discontinued before study drug administration according to the patient's request.

rate of nalmefene 20 mg was 80.8%. The administration rate of nalmefene 20 mg was 80.2% and 86.4% in patients with TEAE ($n = 125$) and those without TEAE ($n = 12$), respectively.

Safety

Long-term safety of nalmefene was evaluated in patients who received a 20 mg dose during the treatment period of both the lead-in and the extension studies ($n = 137$). TEAE that occurred in $\geq 5\%$ of patients during the 48-week treatment period included: nasopharyngitis, nausea, somnolence, and dizziness (Table 2). The TEAE mainly reported during Week 0 to Week 24 decreased during Week 24 to Week 48. TEAE that occurred in $<5\%$ of patients during Week 0 to Week 24 but increased to $\geq 5\%$ during Week 24 to Week 48 included abdominal discomfort, back pain, dysgeusia, and headache. Most TEAE were mild (74.5% and 58.4%) or moderate (10.9% and 11.7%) in severity during Week 0 to Week 24 and Week 24 to Week 48, respectively.

Two (1.5%) patients had serious TEAE, including dehydration and prostate cancer. Eight (5.8%) patients experienced TEAE leading to treatment discontinuation, including abdominal discomfort, nausea, malaise, aspartate aminotransferase increased, GGT increased, dehydration, systemic lupus erythematosus, prostate

cancer, dizziness, headache, and insomnia. The incidence rate of each TEAE leading to discontinuation was 0.7%. No deaths were reported in this study.

The safety during the run-out period (nalmefene 20 mg, $n = 172$; placebo, $n = 171$) and follow-up period (nalmefene 20 mg, $n = 171$; placebo, $n = 171$) was evaluated in patients who completed the 24-week treatment period of this extension study. TEAE were reported during the run-out period, most of which were of mild or moderate severity (Table 3). Serious TEAE included a case of thrombotic cerebral infarction in the nalmefene 20 mg group and a case of organizing pneumonia in the placebo group. One patient receiving nalmefene 20 mg in the run-out period developed an increase in ALT that led to nalmefene discontinuation.

During the follow-up period, TEAE were reported in 18.7% and 12.9% of patients assigned to the nalmefene 20 mg and placebo groups in the run-out period, respectively. No serious TEAE were observed during this period.

No clinically significant laboratory findings or clinically relevant changes in vital signs, bodyweight, or electrocardiogram parameters were observed during the treatment, run-out, or follow-up periods, except for an increase in ALT in one patient in the run-out period.

The dependence assessment during the run-out period did not show any differences between the nalmefene 20 mg and placebo

Table 1 Baseline characteristics of the patients

Baseline characteristics	Nalmefene 20 mg, [†] SS (<i>n</i> = 137), FAS (<i>n</i> = 137)	Total, [‡] SS (<i>n</i> = 403), FAS (<i>n</i> = 400)
	Age, years	50.0 ± 11.7
Sex, <i>n</i> (%)		
Male	104 (75.9)	287 (71.2)
BMI, kg/m ²	22.81 ± 3.21	23.26 ± 3.47
Smoking history, <i>n</i> (%)		
Never smoked	36 (26.3)	104 (25.8)
Current smoker	39 (28.5)	108 (26.8)
No drug abuse history, <i>n</i> (%)	137 (100.0)	403 (100.0)
Marital status, <i>n</i> (%)		
Married	99 (72.3)	293 (73.3)
Employment status, <i>n</i> (%)		
Employed	110 (80.3)	331 (82.8)
CIWA-Ar (summary score at randomization)	0.4 ± 1.1	0.4 ± 1.0
SF-36		
PCS	52.45 ± 6.87	52.81 ± 7.22
MCS	52.63 ± 8.38	52.12 ± 8.18
Age at onset of drinking, years	37.4 ± 13.9	37.1 ± 12.5
WHO drinking risk level, <i>n</i> (%)		
Very high	61 (44.5)	180 (45.0)
High	76 (55.5)	220 (55.0)
HDD, days/month	22.54 ± 6.70	23.04 ± 6.32
TAC, g/day	94.10 ± 34.43	93.35 ± 36.90
CGI-S	3.46 ± 0.95	3.46 ± 1.06
GGT, IU/L	80.0 ± 104.7	75.0 ± 88.0
ALT, U/L	23.1 ± 12.9	23.6 ± 14.7
Previously treated for alcohol dependence, <i>n</i> (%)	2 (1.5)	8 (2.0)
Previously treated for alcohol withdrawal, <i>n</i> (%)	0	0
Family history of alcohol problems, <i>n</i> (%)	21 (15.3)	54 (13.4)

Values are presented as mean ± SD, unless otherwise stated.

[†]Patients treated with nalmefene 20 mg throughout the 48-week period consist of the treatment period of both lead-in and extension study.

[‡]Patients treated with nalmefene 20 mg (*n* = 137), nalmefene 10 mg (*n* = 94), or placebo (SS, *n* = 172; FAS, *n* = 169) during Week 0 to Week 24 followed by nalmefene 20 mg from Week 24 to Week 48. FAS data are indicated for marital status, employment status, SF-36 PCS, SF-36 MCS, drinking risk level, HDD, TAC, CGI-S, GGT, and ALT.

ALT, alanine transaminase; BMI, body mass index; CGI-S, Clinical Global Impressions – Severity; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol – Revised; FAS, full analysis set; GGT, gamma-glutamyltransferase; HDD, heavy drinking days; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-36, Short Form-36; SS, safety data set; TAC, total alcohol consumption; WHO, World Health Organization.

groups, and no withdrawal symptoms were observed during the follow-up period (Tables S1 and S2).

Table 2 TEAE occurring in ≥5% with nalmefene 20 mg during the lead-in study, the extension study, and the total treatment period

TEAE, <i>n</i> (%)	Nalmefene 20 mg (<i>n</i> = 137)		
	Treatment period		
	Lead-in study (Week 0 to Week 24)	Extension study (Week 24 to Week 48)	Total (Week 0 to Week 48)
Total TEAE	117 (85.4)	96 (70.1)	125 (91.2)
Nasopharyngitis	33 (24.1)	23 (16.8)	51 (37.2)
Nausea	38 (27.7)	21 (15.3)	50 (36.5)
Somnolence	26 (19.0)	9 (6.6)	29 (21.2)
Dizziness	19 (13.9)	8 (5.8)	23 (16.8)
Malaise	15 (10.9)	7 (5.1)	20 (14.6)
Vomiting	12 (8.8)	6 (4.4)	17 (12.4)
Insomnia	9 (6.6)	2 (1.5)	11 (8.0)
Constipation	8 (5.8)	2 (1.5)	10 (7.3)
Abdominal distension	8 (5.8)	3 (2.2)	11 (8.0)
Abdominal discomfort	6 (4.4)	9 (6.6)	12 (8.8)
Decreased appetite	6 (4.4)	4 (2.9)	10 (7.3)
Feeling abnormal	5 (3.6)	3 (2.2)	7 (5.1)
Blood prolactin increased	5 (3.6)	2 (1.5)	7 (5.1)
Middle insomnia	5 (3.6)	2 (1.5)	7 (5.1)
Headache	4 (2.9)	8 (5.8)	12 (8.8)
Diarrhea	4 (2.9)	6 (4.4)	7 (5.1)
Back pain	3 (2.2)	8 (5.8)	11 (8.0)
Dysgeusia	2 (1.5)	7 (5.1)	8 (5.8)

TEAE, treatment emergent adverse events.

No patients showed suicidal ideation or suicidal behavior according to the C-SSRS evaluation during the treatment or run-out periods.

Efficacy

The long-term efficacy of nalmefene was evaluated in patients who received nalmefene 20 mg during both the lead-in and the extension studies (*n* = 137). Overall, the number of HDD and TAC decreased from baseline to 48 weeks (MMRM, least squares [LS mean] ± standard error [SE], HDD: -15.09 ± 0.77 days/month and TAC: -53.20 ± 2.29 g/day) during the study (Fig. 2 and Table 4). The reductions in the number of HDD and TAC in the nalmefene 20 mg group were observed from Week 4 and were sustained throughout the 48-week period.

In the placebo group, which was switched to nalmefene 20 mg at Week 24, the number of HDD changed from -8.83 ± 0.72 days/month at Week 24 to -14.39 ± 0.67 days/month at Week 28. TAC changed from -34.13 ± 2.11 g/day at Week 24 to -50.37 ± 2.06 g/day at Week 28. The reductions in the number of HDD and TAC observed at Week 28 were sustained during the 24-week treatment period.

The proportions of patients with RSDRL, RLDRL, TAC70, and HDD response in the nalmefene 20 mg group at Week 24 were 43.8%, 27.0%, 19.7%, and 29.2%, respectively. These responses were sustained at Week 48 (Table 5).

The CGI-S, CGI-I, and AQoLS scores were improved in the nalmefene 20 mg group from Week 0 to Week 24 and these improvements continued to Week 48 (Table S3), while no changes from baseline were observed in the SF-36 and EQ5D scores during the

Table 3 TEAE occurring in ≥1% of patients in the run-out period

TEAE, n (%)	Nalmefene 20 mg [†] (n = 172)	Placebo [‡] (n = 171)
Total TEAE	30 (17.4)	20 (11.7)
Nasopharyngitis	7 (4.1)	1 (0.6)
ALT increased	1 (0.6)	2 (1.2)
Blood prolactin increased	1 (0.6)	2 (1.2)
Blood triglycerides increased	2 (1.2)	2 (1.2)
ECG QT prolonged	2 (1.2)	0
GGT increased	1 (0.6)	3 (1.8)
Musculoskeletal stiffness	2 (1.2)	0

[†]Patients treated with nalmefene 20 mg during the 4-week run-out period.

[‡]Patients treated with placebo during the 4-week run-out period. ALT, alanine aminotransferase; ECG, electrocardiogram; GGT, gamma-glutamyltransferase; TEAE, treatment emergent adverse events.

48-week treatment period (Table S4). A reduction in the serum GGT and ALT levels was observed in the nalmefene 20 mg group at Week 24, which continued to Week 48 (Table S5).

The efficacy of nalmefene in the run-out period was evaluated in patients (nalmefene 20 mg, n = 172; placebo, n = 171) who completed the 24-week treatment period of this extension study. The number of HDD and TAC values were similar in the nalmefene 20 mg and placebo groups during this period (Table 6).

Discussion

This was the first prospective study to evaluate the long-term safety and efficacy of nalmefene 20 mg in Japanese patients with a high or very high DRL of alcohol dependence. Long-term nalmefene 20 mg was well tolerated during the 48 weeks of treatment in the lead-in and extension studies, with no dependence due to nalmefene or withdrawal symptoms after nalmefene discontinuation. Treatment with nalmefene also reduced the number of HDD and TAC throughout the 48-week treatment period.

The main TEAE with nalmefene 20 mg reported in ≥5% of patients during the 48-week treatment period included dizziness, nasopharyngitis, nausea, malaise, vomiting, and somnolence. In the 52-week SENSE study,¹² dizziness, nasopharyngitis, nausea,

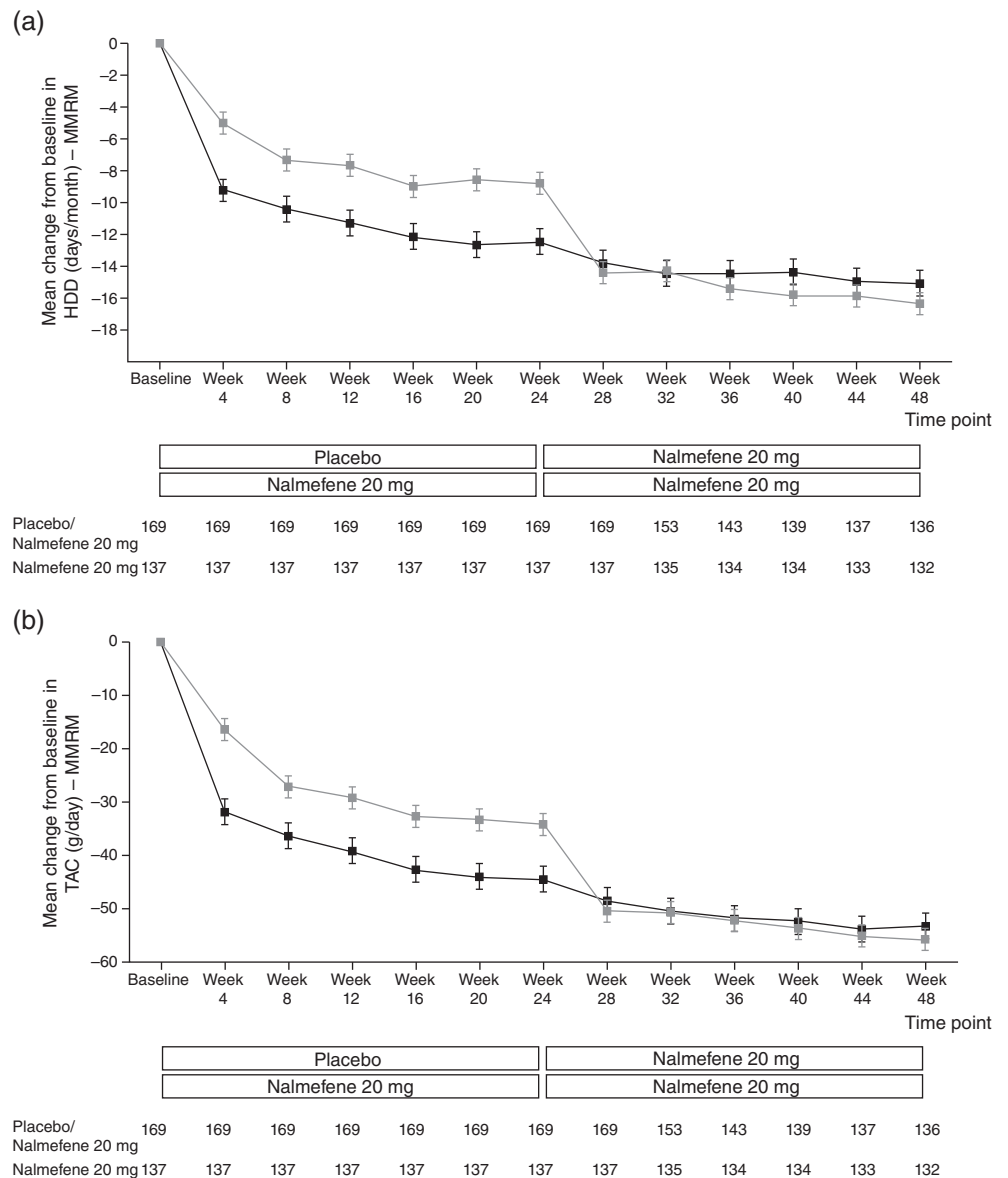


Fig.2 Change from baseline by treatment group (nalmefene 20 mg vs placebo) in the (a) number of heavy drinking days (HDD; days/month) and (b) total alcohol consumption (TAC; g/day). Data obtained using mixed model for repeated measures (MMRM) analysis of the full analysis set. Values presented as least squares mean ± standard error. The number of patients at each time point is shown below the x-axis. Nalmefene 20 mg group: patients treated with nalmefene 20 mg throughout the 48-week treatment period; placebo/nalmefene group: patients treated with placebo during Week 0 to Week 24 followed by nalmefene 20 mg during Week 24 to Week 48 (—■— Placebo/nalmefene 20 mg and —●— Nalmefene 20 mg).

Table 4 Mean change in the number of HDD and TAC during the treatment period

	HDD, days/month				TAC, g/day				
	Baseline	Week 24	Week 28	Week 48	Baseline	Week 24	Week 28	Week 48	
Nalmefene 20 mg [†]	<i>n</i>	137	137	137	132	137	137	137	132
	Mean ± SD	22.54 ± 6.70	10.79 ± 9.04	9.58 ± 9.16	8.23 ± 9.59	94.10 ± 34.43	52.54 ± 32.41	48.50 ± 33.03	43.75 ± 30.71
Placebo/nalmefene 20 mg [‡]	<i>n</i>	169	169	169	136	169	169	169	136
	Mean ± SD	22.70 ± 6.54	14.31 ± 10.01	8.82 ± 8.52	6.73 ± 8.42	92.30 ± 41.03	60.68 ± 28.84	44.51 ± 27.18	39.79 ± 26.69
Change from baseline									
Nalmefene 20 mg [†]	Mean		-11.75	-12.96	-14.25		-41.56	-45.60	-50.40
	95%CI		-13.37, -10.13	-14.60, -11.33	-15.90, -12.59		-47.17, -35.94	-51.23, -39.97	-55.70, -45.10
Change from Week 24									
Placebo/nalmefene 20 mg [‡]	Mean			-5.49	-7.82			-16.17	-22.85
	95%CI			-6.68, -4.31	-9.35, -6.29			-19.42, -12.91	-26.67, -19.03
Adjusted change from baseline [§]									
Nalmefene 20 mg [†]	LS mean (SE)		-12.48 (0.81)	-13.80 (0.76)	-15.09 (0.77)		-44.44 (2.40)	-48.45 (2.35)	-53.20 (2.29)
Placebo/nalmefene 20 mg [‡]	LS mean (SE)		-8.83 (0.72)	-14.39 (0.67)	-16.35 (0.70)		-34.13 (2.11)	-50.37 (2.06)	-55.77 (2.06)

[†]Patients treated with nalmefene 20 mg throughout 48-week period.

[‡]Patients treated with placebo during Week 0 to Week 24 followed by nalmefene 20 mg during Week 24 to Week 48.

[§]Derived using mixed model for repeated measures (MMRM) approach with fixed effect of treatment, sex, time point, treatment-by-time-point interaction, baseline value, baseline value-by-time-point interaction with an unstructured variance-covariance matrix structure. Data for nalmefene 20 mg and placebo groups were calculated using MMRM analysis of the FAS, which included patients treated with nalmefene 20 mg, nalmefene 10 mg, and placebo.

CI, confidence interval; HDD, heavy drinking days; LS, least squares; SD, standard deviation; SE, standard error; TAC, total alcohol consumption.

vomiting, insomnia, and somnolence were highly expressed (>8%) in the nalmefene-treated groups. Therefore, the long-term safety profile of nalmefene was similar in this extension study to the previous study.¹²

In the present study, no dependence symptoms due to nalmefene itself were observed. This may be attributed to the pharmacological activity of nalmefene as an opioid antagonist of the μ and δ receptors and a partial agonist of the κ receptor, which do not activate the reward circuits in the brain associated with dependence.¹⁸

In the lead-in study conducted as a randomized controlled trial, compared with placebo, nalmefene was associated with significant reductions in HDD at Week 12 (difference in 20 mg group, -4.34 days/month; 95%CI: -6.05 to -2.62; $P < 0.0001$; difference in

10 mg group, -4.18 days/month; 95%CI: -6.05 to -2.32; $P < 0.0001$), as well as a significant reduction in TAC at Week 12 ($P < 0.0001$).¹³ Regarding the changes from baseline during the 48-week treatment period, treatment with nalmefene 20 mg reduced the number of HDD and TAC at Week 24 (MMRM, LS mean ± SE, HDD: -13.25 ± 0.66 days/month and TAC: -49.43 ± 2.13 g/day).¹³ These reductions in the number of HDD and TAC from baseline were sustained throughout the extension study. Patients who received placebo in the lead-in study started treatment with nalmefene 20 mg in the extension study. Although they had not been exposed to nalmefene for 24 weeks in the lead-in study, the number of HDD and TAC decreased 4 weeks after the start of nalmefene administration at Week 24 and these reductions were sustained until Week 48. The

Table 5 Proportion of patients with RSDRL, RLDRL, TAC 70, and HDD response during the treatment period

	<i>n</i>	RSDRL, [†] <i>n</i> (%)	RLDRL, <i>n</i> (%)	TAC 70, <i>n</i> (%)	HDD response, <i>n</i> (%)
Week 24					
Nalmefene 20 mg [‡]	137	60 (43.8)	37 (27.0)	27 (19.7)	40 (29.2)
95%CI [¶]		35.5, 52.1	19.6, 34.4	13.0, 26.4	21.6, 36.8
Placebo/nalmefene 20 mg [§]	169	39 (23.1)	27 (16.0)	12 (7.1)	37 (21.9)
95%CI [¶]		16.7, 29.4	10.5, 21.5	3.2, 11.0	15.7, 28.1
Week 48					
Nalmefene 20 mg [‡]	132	76 (57.6)	60 (45.5)	39 (29.5)	69 (52.3)
95%CI [¶]		49.1, 66.0	37.0, 53.9	21.8, 37.3	43.8, 60.8
Placebo/nalmefene 20 mg [§]	136	78 (57.4)	58 (42.6)	49 (36.0)	78 (57.4)
95%CI [¶]		49.0, 65.7	34.3, 51.0	28.0, 44.1	49.0, 65.7

[†]Shift from very high drinking risk level at baseline to medium drinking risk level or below, or from high drinking risk level at baseline to low drinking risk level or below.

[‡]Patients treated with nalmefene 20 mg throughout the 48-week period.

[§]Patients treated with placebo during Week 0 to Week 24 followed by nalmefene 20 mg during Week 24 to Week 48.

[¶]Values are shown as the 95%CI of the percentage at each time point on Week 24 or Week 48.

CI, confidence interval; HDD, heavy drinking days; RLDRL, response low drinking risk level; RSDRL, response shift drinking risk level; TAC 70, 70% decrease in total alcohol consumption.

Table 6 Mean change in the number of HDD and TAC during the run-out period

		HDD, days/month		TAC, g/day	
		Baseline	Week 4	Baseline	Week 4
Nalmefene 20 mg [†]	<i>n</i>	172	172	172	172
	Mean ± SD	7.06 ± 8.66	7.68 ± 9.10	39.05 ± 27.28	38.96 ± 28.60
Placebo [‡]	<i>n</i>	171	171	171	171
	Mean ± SD	7.67 ± 9.16	8.77 ± 9.81	43.36 ± 29.60	44.92 ± 31.66
Change from baseline					
Nalmefene 20 mg [†]	Mean		0.62		-0.09
	95%CI		-0.09, 1.32		-1.72, 1.55
Placebo [‡]	Mean		1.10		1.56
	95%CI		0.43, 1.78		0.07, 3.04
Adjusted change from baseline [§]					
Nalmefene 20 mg [†]	LS mean (SE)		0.68 (0.36)		-0.18 (0.82)
Placebo [‡]	LS mean (SE)		1.27 (0.38)		1.43 (0.88)

Baseline is Week 24 of treatment period during the extension study.

[†]Patients treated with nalmefene 20 mg during the 4-week run-out period after completing treatment with nalmefene 20 mg during the 24-week period.

[‡]Patients treated with placebo during the 4-week run-out period after completing treatment with nalmefene 20 mg during the 24-week period.

[§]Calculated using analysis of covariance model with treatment and sex in the run-out period of extension study as fixed, categorical effect and number of HDD and TAC at baseline as covariance.

HDD, heavy drinking days; LS, least squares; SD, standard deviation; SE, standard error; TAC, total alcohol consumption.

mean administration rate with nalmefene 20 mg during the 48-week treatment period was 80.8% compared with 70.6% observed with nalmefene 20 mg during the lead-in study.¹³ It may be assumed that patients registered in the extension study are those who have a stronger intention to reduce drinking, which may have influenced the results.

As long-term abstinence retention rates are relatively low according to a study conducted in Japan,¹⁹ treatment options with long-term tolerability are needed. The results of the present study suggest the 48-week efficacy and tolerability of nalmefene treatment in patients with alcohol dependence; however, further research, including real-world studies, is warranted. In addition, as there has been discussion as to whether nalmefene treatment could provide harm reduction or improvement of quality of life in patients with alcohol dependence,²⁰ studies evaluating these outcomes should also be conducted.

This study had some limitations. First, the results of the long-term safety and efficacy of nalmefene 20 mg were not based on a statistical comparison with placebo during the 48-week period, as the 24-week treatment period in the extension study was designed as an open-label uncontrolled study following the 24-week placebo-controlled lead-in study. Second, because all patients in this study were Japanese, extrapolating the results of this study to other patient populations may be limited.

In conclusion, long-term treatments for abstinence and reduction in alcohol consumption are needed because patients treated for alcohol dependence are at constant risk of relapse. The present study showed that long-term treatment with nalmefene 20 mg was safe and effective in Japanese patients with high or very high DRL of alcohol dependence. This result might provide additional information for experts to consider a drinking-reduction-oriented approach as a treatment option for alcohol dependence.

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Author contributions

S.H., M.T., Y.M., K.T., and H.M. conceived and designed the study, and were involved in data acquisition. K.T. was the study statistician. D.M. contributed to the study design, data interpretation, preparation of the study report, writing the manuscript, and reading and approving the drafts. All authors participated in the interpretation of data, manuscript writing, critical review, and revising the manuscript. All authors approved the final manuscript for publication.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Study assessments: Dependence and withdrawal assessment.

Fig. S1. Treatment schedule.

Table S1. Dependence assessment during the run-out period.

Table S2. Withdrawal assessment during the follow-up period.

Table S3. Mean change in Clinical Global Impression – Severity of Illness, Clinical Global Impression – Global Improvement, and Alcohol Quality of Life Scale scores during the treatment period.

Table S4. Mean change in Short Form-36 Physical Component Summary and Mental Component Summary, and EuroQol 5 Dimension scores during the treatment period.

Table S5. Mean change in γ -glutamyltransferase and alanine aminotransferase during the treatment period.