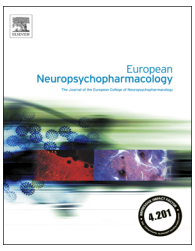
European Neuropsychopharmacology (2013) 23, 1432–1442



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A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence

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Received 16 October 2012; received in revised form 17 January 2013; accepted 28 February 2013

KEYWORDS
Alcohol dependence;
Harm-reduction;
Nalmefene;
Opioid antagonist;
As-needed;
Treatment

Abstract
This study evaluated the efficacy of as-needed use of the opioid system modulator nalmefene in reducing alcohol consumption in patients with alcohol dependence. Seven hundred and eighteen patients (placebo=360; nalmefene=358), ≥18 years of age, with a diagnosis of alcohol dependence, ≥6 heavy drinking days and an average alcohol consumption ≥WHO medium drinking risk level in the 4 weeks preceding screening, were randomised (1:1) to 24 weeks of as-needed placebo or nalmefene 18 mg/day.
The co-primary efficacy analyses showed a significantly superior effect of nalmefene compared to placebo in the change from baseline to month 6 in heavy drinking days (group difference: −1.7 days/month [95% CI −3.1; −0.4]; p=0.012) and a better but not significant effect in reducing total alcohol consumption (group difference: −5.0 g/day last month [95% CI −10.6; 0.7]; p=0.088). A subgroup analysis showed that patients who did not reduce their drinking prior to randomisation benefitted more from nalmefene. Improvements in Clinical Global Impression and reductions in liver enzymes were greater in the nalmefene group than in the placebo group. Adverse events were more common with nalmefene; the incidence of adverse events leading to dropout was similar in both groups.
This study provides evidence for the efficacy of nalmefene, which constitutes a new pharmacological treatment paradigm in terms of treatment goal (reduced drinking) and dosing regimen (as-needed), in alcohol dependent patients unable to reduce alcohol consumption on their own.

1. Introduction

Europe has the highest overall consumption of alcohol (World Health Organization, 2010), and in general, the European Union can be characterised by a lower proportion of abstainers

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http://dx.doi.org/10.1016/j.euroneuro.2013.02.006

and a higher proportion of the population drinking more than 20 g of pure alcohol per day than the rest of the world (World Health Organization, 2011). Worldwide, the European region suffers the highest impact of alcohol with 6.5% of all deaths and 11.6% of all disability-adjusted life years attributable to alcohol (Rehm et al., 2009).

Most of the alcohol-attributable mortality is due to alcohol dependence, presumably by means of heavy drinking (Rehm et al., 2013). Approximately 15 million persons in the European Union are alcohol-dependent (Wittchen et al., 2011). There is a large treatment gap, with less than 10% of people in Europe with a diagnosis of any alcohol disorder (including alcohol dependence) actually receiving any treatment (Alonso et al., 2004).

Reduction of alcohol consumption is increasingly accepted as a viable treatment goal (European Medicines Agency, 2010; Luquiens et al., 2011). However, the three currently registered pharmacological treatments for alcohol dependence are indicated only for the maintenance of abstinence following detoxification.

A large proportion of patients in abstinence-oriented treatments experience relapses (Anton et al., 2006; Mann et al., 2004; Merkx et al., 2011; Miller et al., 2001), and abstinence-oriented treatments might not be desirable or acceptable to many patients (Gastfriend et al., 2007; Marlatt and Witkiewitz, 2002). Allowing patients to choose between abstinence and reduced drinking as their treatment goal may enhance engagement with the treatment, ultimately leading to better treatment outcomes for the population at large (Adamson et al., 2010; Heather et al., 2010). Furthermore, research has shown that any reduction in alcohol consumption for a person who consumes more than 10 g of alcohol per day will reduce the annual and lifetime risk of alcohol-related death (Rehm et al., 2011).

Therefore, there is clearly a need for new pharmacological treatments allowing for reduction of alcohol consumption as a treatment goal.

Nalmefene is an opioid system modulator, which in several studies in patients with alcohol use disorders has been associated with a reduction of heavy drinking. Although Anton et al. (2004) were unable to show a reduction in alcohol use compared to placebo, other studies in patients with alcohol-use disorders indicate that treatment with nalmefene causes a reduction of heavy drinking (Karhuvaara et al., 2007; Mason et al., 1994, 1999). A recently published large phase 3 study in patients with alcohol dependence showed that nalmefene, taken on an as-needed basis was superior to placebo in reducing alcohol consumption (Mann et al., 2013).

Here, we present results from another recently completed phase 3 study in patients with alcohol dependence that assessed the efficacy and safety of as-needed use of nalmefene in reducing alcohol consumption, measured as the monthly changes from baseline in the number of heavy drinking days (days in last month) and mean total alcohol consumption (g/day in last month) during a treatment period of 24 weeks.

2. Experimental procedures

2.1. Patients

This randomised, double-blind, placebo-controlled, parallel-group study included patients from 57 sites in Belgium, the Czech Republic, France, Italy, Poland, Portugal, and Spain. Patients were recruited from in- and out-patient clinics, from the study site's patient pool, and by spontaneous referrals to the study site. Advertisements were used in the Czech Republic, France, Italy, and Spain. Eligible patients were men and women aged ≥18 years with a primary diagnosis of alcohol dependence according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR™ [American Psychiatric Association, 2000]) (assessed using the Mini-International Neuropsychiatric Interview [MINI; Lecrubier et al., 1997]) and a blood alcohol concentration <0.02% at the screening visit. Exclusion criteria were (a) <6 heavy drinking days in the 4 weeks before screening (European Medicines Agency, 2010; a day with alcohol consumption ≥60 g for men and ≥40 g for women), (b) an average alcohol consumption below medium drinking risk level according to the World Health Organization (WHO) in the 4 weeks before screening (≤40 g alcohol/day for men and ≤20 g alcohol/day for women; World Health Organization, 2000), (c) >14 consecutive abstinent days in the 4 weeks preceding screening, (d) a score ≥10 on the revised version of the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar; Sullivan et al., 1989), indicating the need for medication supported detoxification, (e) aspartate aminotransferase or alanine aminotransferase (ALAT) values >3 times of upper normal limit, (f) a current DSM-IV Axis I disorder other than alcohol dependence (except nicotine dependence), (g) a DSM-IV Axis II antisocial personality disorder (assessed using the MINI) or (h) recent (within 1 week prior to the screening visit) treatment with opioid agonists or partial agonists. For the full list of selection criteria, see Supplementary material.

This study was designed and conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice, and each site started patient inclusion only after ethics committee approval. All patients gave written informed consent.

2.2. Randomisation and blinding

At baseline (week 0), eligible patients were assigned to 24 weeks of treatment with as-needed use of either placebo or nalmefene 18 mg (base) in a 1:1 ratio, according to a computer generated randomisation list (in blocks of 4), provided by the sponsor. Randomisation for the run-out period was also done at baseline.

Patients, investigators, staff and the sponsor were blind to treatment assignment. Two sets of sealed envelopes containing study medication details for each patient were prepared. One set was kept by the sponsor and one set by the investigator or pharmacist. The randomisation code was only to be broken by the investigator in case of an emergency situation. The randomisation code was not broken for any patient during the study. Nalmefene and placebo tablets were identical in appearance.

2.3. Procedures

The study consisted of a 1 to 2-week screening period, a 24-week double-blind main treatment period with nalmefene or placebo, and a 4-week double-blind run-out period (to evaluate any treatment discontinuation effects) during which nalmefene-treated patients were randomised to placebo or nalmefene (1:1) and placebo-treated patients continued with placebo. A safety follow-up was scheduled 4 weeks after completion or dropout.

Patients were instructed to take one tablet on each day they perceived a risk of drinking alcohol (as-needed dosing), preferably 1–2 h prior to the anticipated time of drinking. Tablets could be taken up to once daily and were supplied in wallet cards with space for the patient to record the date of study medication intake. The Timeline Follow-back (Sobell and Sobell, 1992) was used to obtain estimates of daily drinking as well as to record daily medication intake. In addition, all patients took part in a motivational and adherence-enhancing intervention (BRENDA [Volpicelli et al., 2001;

Starosta et al., 2006]) to support them in changing their behaviour and to enhance adherence to treatment, starting at randomisation and subsequently at all scheduled visits. No treatment goal was defined, i.e. both abstinence and reduction were accepted; no information was collected on individual treatment goals. Measurements needed for the assessment of efficacy and safety were performed at screening (week-1 or week-2), baseline, weeks 1, 2, and 4, followed by monthly assessments. For a full description of timing of assessments, the reader is referred to the Supplementary material.

Monthly drinking variables were derived from the Timeline Follow-back (Sobell and Sobell, 1992) that provided information of daily number of standard drinks. To define standard drinks, a conversion card was provided. The conversion of recorded standard drinks to grams was performed by a statistical programmer using the following country specific factors:: Belgium, Italy, Poland, and Spain 10 g; France 12 g; Portugal 14 g; Czech Republic 16 g.

At screening, patients reported their daily drinking over the previous month (=28 consecutive days). At subsequent visits, they reported drinking since the previous visit.

The pre-defined co-primary outcome measures were change from baseline in heavy drinking days and change from baseline in total alcohol consumption (g/day) at month 6.

Key-secondary outcome measure was drinking risk level response (from very high drinking risk level at baseline to medium drinking risk level or below, or from high or medium drinking risk level at baseline to low drinking risk level or below) at month 6.

Secondary outcome measures reported here are Clinical Global Impression-Severity of Illness (CGI-S) and Global Improvement (CGI-I) scores (Guy, 1976) and γ-glutamyltransferase (GGT) and ALAT values at week 24. Other secondary variables will be reported elsewhere. For the full list of outcome variables, the reader is referred to the Supplementary material.

Clinical status was based on Clinical Global Impression-Severity of Illness, the Alcohol Dependence Scale (Skinner and Horn, 1984), and the Drinker Inventory of Consequences (Miller et al., 1995).

Safety assessments consisted of evaluation of adverse events (including pre-treatment and treatment-emergent adverse events), clinical safety laboratory tests, vital signs, weight, electrocardiograms, and Profile of Mood States. To capture any signal related to psychiatric adverse events, a group of selected adverse events was pre-defined (see Supplementary material). Adverse events potentially related to suicide were identified using the sub-standardised Medical Dictionary for Regulatory Activities query "suicide/self-injury".

2.4. Statistical analysis

The sample size calculation was based on a standard deviation for the change from baseline in number of heavy drinking days of 7 days and the change from baseline in total alcohol consumption of 36.5 g/day and a correlation of 0.7 between heavy drinking days and total alcohol consumption. With a significance level of 5%, 300 patients in each treatment group would provide a power of 90% for detecting a difference between the treatment groups of three heavy drinking days and 12 g/day in the total alcohol consumption, accounting for an expected drop-out rate of 35% at month 6.

Three datasets were pre-specified in the study protocol:

The *all-patients-randomised set*, comprising all randomised patients, was used to calculate the incidence of serious adverse events, in order to account for any pre-treatment serious adverse events.

The *all-patients-treated set*, comprising all randomised patients but excluding from the dataset those with no recorded study medication intake and all study medication returned. This dataset was used for all remaining safety analyses.

The *full-analysis set*, comprising all patients in the *all-patients-treated set* with at least one valid post-baseline assessment of alcohol consumption, was used for all efficacy analyses.

Baseline for drinking variables in the main treatment period was defined as the month preceding the screening visit. For all other variables, baseline was defined as the assessment at the screening visit.

The co-primary outcome measures were analysed using mixed model repeated measures, using observed cases, with the baseline score as covariate, and site, sex, time (months 1–6), and treatment as fixed effects; baseline score-by-time interaction and treatment-by-time interaction were also included in the model.

Sensitivity analyses were performed using analysis of covariance by month with the same covariates and fixed effects as in the mixed model repeated measures analysis, using (a) observed cases, (b) last observation carried forward and baseline observation carried forward imputation, (c) placebo mean imputation (imputing the month one estimation in the placebo group to all time points with missing data) and (d) multiple imputation assuming that the future behaviour of withdrawn patients is the same as those in the placebo group with a similar past (Little and Yau, 1996).

Post-hoc analyses of the co-primary variables were performed to estimate the effect of nalmefene versus placebo in the subgroup of patients who, reduced or did not reduce their drinking to less than 6 heavy drinking days per month or below medium drinking risk level already in the period between screening and randomisation. All patients were classified as having (yes/no) at least a medium drinking risk level and at least 6 heavy drinking days in the period between screening and randomisation (extrapolated to 4 weeks). These analyses were performed using the primary mixed model repeated measures model including alcohol consumption at randomisation (yes/no)-by-time-by-treatment interaction with randomisation score as response assuming no systematic difference between the treatment groups.

The null hypothesis of no difference in treatment effect on heavy drinking days and total alcohol consumption had to be rejected in order to proceed with formal testing of the key-secondary outcome measure, which was analysed by logistic regression by month, with country, sex, baseline drinking risk level, and treatment as fixed effects, imputing missing values with response based on mixed model repeated measures—predicted total alcohol consumption values from the primary analysis.

The odds ratio of nalmefene compared to placebo with 95% confidence interval and corresponding *p*-value based on the likelihood ratio test was estimated from the model. Sensitivity analyses were performed for the same logistic regression model using observed cases, last observation carried forward, non-response or sustained response imputation for missing values, where sustained response was defined as response at the current month and response at the previous month with LOCF imputation for missing values.

The secondary outcome measures (CGI-S, CGI-I, log-transformed GGT and ALAT values) were analysed with similar models as used for the co-primary variables. The CGI-S baseline score was included as a covariate in the model for CGI-I.

Adverse events were coded using the lowest level term according to Medical Dictionary for Regulatory Activities, Version 13.0.

The principal statistical software used was SAS®, Version 9.2.

3. Results

3.1. Study sample

From March, 2009 to July, 2010, 941 patients were screened, of whom 718 were randomised (Figure 1). There were no clinically relevant differences in baseline demographic or clinical characteristics between the groups (Table 1). All but eight patients were Caucasian, approximately 70% were men, and the mean

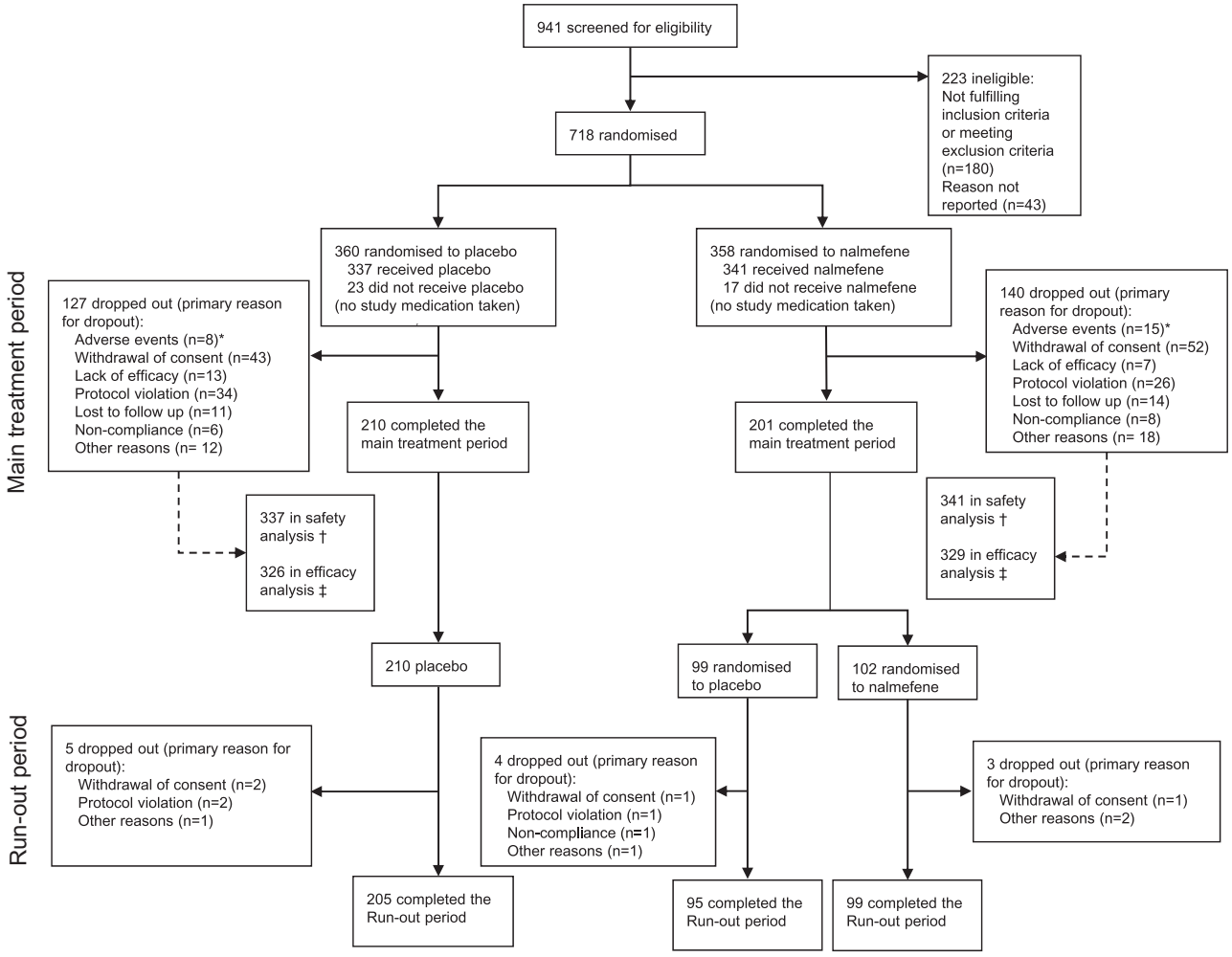

Figure 1 Trial profile. *Adverse events were not set to primary reason for dropout by default. †=*All-patients-treated set*, comprising all randomised patients but excluding from the dataset those with no recorded study medication intake and all study medication returned. ‡=*Full-analysis set*, comprising all patients in the *all-patients-treated set* with at least one valid post-baseline assessment of alcohol consumption. Eleven (11) and twelve (12) patients in the placebo and nalmefene groups, respectively were not included in the *full-analysis set*.

age was 45 years. Mean age of onset of alcohol problems was 32 years.

In the month before screening, patients had on average 19 heavy drinking days and drank on average 90 g of alcohol per day. The mean CGI-S score of 4, the Drinker Inventory of Consequences score of 46, and the Alcohol Dependence Scale score of approximately 14 confirmed that these were moderately ill patients with significant adverse consequences of drinking. Mean values of liver parameters were close to or slightly above the reference ranges. The majority of patients had not previously been treated for either alcohol dependence (429 [60%] of 718) or alcohol withdrawal symptoms (593 [83%] of 718).

The *all-patients-treated set* comprised 678 patients and the *full-analysis set* comprised 655 patients. Importantly, 218 of these patients (33%) reduced their drinking to <6 heavy drinking days/month or below medium drinking risk level already in the period between screening and randomisation, i.e., prior to taking any study medication (Table 1). Baseline characteristics for the patients reducing their consumption prior to treatment initiation were similar to those that did not do so (Supplementary material). However, the early reducers had somewhat lower alcohol consumption as shown by the parameters total alcohol consumption and heavy drinking days, and more often fell within the medium drinking risk level category. During the main treatment period, 127 (38%) of the placebo-treated patients and 140 (41%) of the nalmefene-treated patients dropped out from the study; the most frequent primary reason was withdrawal of consent in both the placebo and nalmefene groups (Figure 1). Two hundred and five patients (61%) in the placebo and 194 (57%) in the nalmefene group completed the entire study.

On average, patients on placebo took study medication on 65% of the days in the main treatment period, whereas patients on nalmefene took study medication on 57% of the days (Table 2).

3.2. Efficacy

The mean number of heavy drinking days decreased from 20 to 7 days/month and the mean total alcohol consumption

Table 1 Demographics and baseline clinical characteristics.

Patients randomised (APRS)		Placebo	Nalmefene
		360	358
Race	Caucasian	357 (99.2%)	353 (98.6%)
Sex	Women	104 (28.9%)	92 (25.7%)
Age (years)		44.4 (10.7)	45.1 (10.7)
Body mass index (kg/m^2)		25.2 (4.2)	25.2 (4.5)
Age at the onset of drinking problems		31.9 (10.9)	32.6 (10.8)
Drinking risk level[a]	Low	6 (1.7%)	5 (1.4%)
	Medium	82 (22.8%)	68 (19.0%)
	High	134 (37.2%)	129 (36.0%)
	Very high	138 (38.3%)	156 (43.6%)
Total monthly heavy drinking days (days)[a]		18.4 (7.0)	19.7 (7.0)
Total alcohol consumption (g alcohol/day)[a]		88.8 (48.2)	92.2 (46.9)
Clinical global impression—severity of illness		3.99 (1.42)	4.05 (1.45)
γ-glutamyltransferase (IU/L)[b]		52.2	51.8
Alanine aminotransferase (IU/L)[b]		28.0	28.7
Mean corpuscular volume (fL)[b]		97.7	97.7
Percentage carbohydrate-deficient transferrin (%)		2.51 (1.35)	2.68 (1.54)
Drinker inventory of consequences total score		46.0 (23.1)	46.7 (23.8)
Alcohol dependence scale total score		14.6 (6.15)	14.5 (5.74)
Living alone	Yes	81 (22.5%)	81 (22.6%)
Unemployed[c]	Yes	84 (25.8%)	76 (23.1%)
Previously treated for alcohol dependence	Yes	147 (40.8%)	142 (39.7%)
Previously treated for alcohol withdrawal	Yes	68 (18.9%)	57 (15.9%)
Family history of alcohol problems	Yes	202 (56.1%)	215 (60.1%)
<6 heavy drinking days or drinking risk level <medium at randomisation[d]	Yes	105 (32.2%)	113 (34.3%)

Data are mean (SD) or number of participants (%).
SD=Standard deviation. APRS=*All-patients-randomised set*.
[a]Based on Timeline Follow-back data from the month preceding the screening visit.
[b]Geometric mean.
[c]Situation at screening. Percentages based on the *full-analysis set*.
[d]Patients having <6 heavy drinking days or a drinking risk level below medium in the period between screening and randomisation, extrapolated to 4 weeks; percentages based on the *full-analysis set*.

Table 2 Distribution of percentage of days with study medication intake in the main treatment period.

Treatment group	Patients	Summary statistics	% of days with study medication[a]
Placebo	333	Mean	65.2
		10th percentile	20.4
		90th percentile	98.8
Nalmefene	337	Mean	57.0
		10th percentile	10.7
		90th percentile	98.8

Only patients in the *all-patients-treated set* with Timeline Follow-back study medication records are included.
[a]Distribution of the individual patient percentages of days with study medication intake.

decreased from 93 to 30 g/day in the nalmefene group at month 6 (Table 3). In the placebo group, the mean number of heavy drinking days decreased from 18 to 8 days/month and the mean total alcohol consumption decreased from 89 to 33 g/day at month 6. A statistically significant reduction in the number of heavy drinking days and total alcohol consumption in favour of nalmefene was observed already at month 1 (Figure 2). The co-primary efficacy analyses showed a statistically significantly superior effect of nalmefene compared to placebo in the change from baseline to month 6 in heavy drinking days (group difference: −1.7 days/month [95% CI −3.1; −0.4]; p=0.012) and a better but not statistically

Table 3 Baseline and month 6 efficacy variables.

Efficacy variable	Placebo		Nalmefene	
	N	Mean±SD	*N*	Mean±SD
Monthly number of heavy drinking days (FAS, OC)				
Baseline	326	18.3±7.0	329	19.8±6.8
Month 6	229	7.5±9.2	212	6.6±8.9
Monthly total alcohol consumption (g/day) (FAS, OC)				
Baseline	326	89±48	329	93±46
Month 6	229	33±38	212	30±36

SD=Standard deviation; FAS=*full-analysis set*; OC=observed cases.

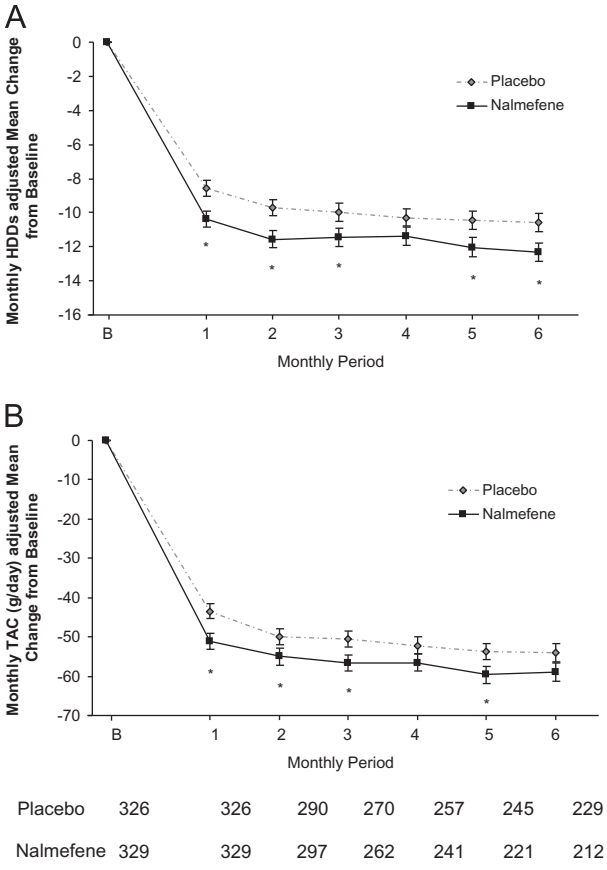

Figure 2 Change in alcohol consumption. (A) Adjusted mean change from baseline in monthly heavy drinking days (HDDs). (B) Adjusted mean change from baseline in monthly total alcohol consumption (TAC; g/day). Baseline data for HDDs and TAC were derived from the Timeline Follow-back for the month preceding the screening visit. Patient numbers contributing to each monthly period are shown below the *x*-axis for each treatment group. *$p<0.05$ (difference to placebo). B=baseline. Bars indicate standard errors.

significant effect in reducing the total alcohol consumption (group difference: −5.0 g/day last month [95% CI −10.6; 0.7]; $p=0.088$) (Table 4). All sensitivity analyses were numerically in favour of nalmefene.

At baseline, the mean number of non-drinking days (standard error) was 5.4±0.3 in the placebo group and 5.0±0.3 in the nalmefene group. The mean number of non-drinking days increased to 14.7±0.7 in the placebo group and to 14.7±0.8 in the nalmefene group at month 6.

The patients (33% [218 of the 655 patients in the full-analysis set]) who in the period between screening and randomisation had reduced the number of heavy drinking days to <6 days/month or had a drinking risk level below medium had reduced their alcohol consumption by 13.9 heavy drinking days and 62.6 g/day at the time of randomisation (Figure 3). In this group, the low level of alcohol consumption was maintained throughout the study with no difference between the treatment groups during the treatment period. However, in the patients (67% [437 of the 655 patients in the full-analysis set]) who in the period between screening and randomisation had ≥6 heavy drinking days/month and at least a medium drinking risk level, nalmefene treatment resulted in a significant reduction compared to placebo in the mean number of heavy drinking days (−2.0 days/month [95% CI −3.6; −0.4]; $p=0.012$) as well as in the mean total alcohol consumption (−7.0 g/day last month [95% CI −13.6; −0.4]; $p=0.037$) at month 6 (Figure 3).

The key secondary outcome measure, analysis of drinking risk level response was numerically in favour of nalmefene (odds ratio=1.28; [0.89; 1.83]; $p=0.1833$ [Table 5]). Similar results were obtained in the sensitivity analyses of the key secondary outcome measure, except for the non-response imputation.

A decrease in the CGI-S score from baseline to week 24 was observed in both treatment groups (Figure 4), with greater mean improvement (group difference: −0.2 [−0.44; −0.02]; $p=0.029$) in the nalmefene group than in the placebo group. The difference in the CGI-I score at week 24 was also in favour of the nalmefene group (group difference: −0.2 [−0.38; 0.04]; $p=0.111$).

For GGT and ALAT, the analysis showed improvements from baseline in both treatment groups; there was a greater reduction from baseline to week 24 in ALAT in the nalmefene group than in the placebo group ($p=0.049$ [Table 6]). There was no difference between nalmefene and placebo in GGT at week 24.

3.3. Safety and tolerability

During the main treatment period, 199 (59%) of the patients in the placebo group and 232 (68%) of the patients in the nalmefene group had treatment-emergent adverse events (Table 7). The majority of these events were *mild* or *moderate*. Approximately half of the patients with treatment-emergent adverse events had treatment-emergent adverse events with an onset within 1 day after the first dose of study medication. Of the most common treatment-emergent adverse events (incidence ≥5%) nausea, dizziness, and insomnia had an incidence two times higher in the nalmefene group than in the placebo group. Fourty three patients dropped out due to treatment-emergent adverse events during the main treatment period: 20 (5.9%) in the placebo group and 23 (6.7%) in the nalmefene group (Table 7). Treatment-emergent adverse events with an incidence ≥0.5%, leading to dropout comprised dizziness, nausea, vomiting, anxiety, and insomnia in the nalmefene

Table 4 Co-primary efficacy analysis at month 6.

Efficacy variable	Adjusted change from baseline to month 6				Difference to placebo	
	Placebo		Nalmefene			
	N	Mean±SE	*N*	Mean±SE	Mean	*p*-value
Number of heavy drinking days (MMRM; OC)	229	−10.6±0.5	212	−12.3±0.5	−1.7 [−3.1; −0.4]	0.012
Number of heavy drinking days—sensitivity analyses						
(ANCOVA; OC)	229	−11.0±0.6	212	−12.9±0.6	−1.9 [−3.4; −0.4]	0.012
(ANCOVA; LOCF)	326	−10.0±0.5	329	−11.8±0.5	−1.8 [−3.0; −0.6]	0.004
(ANCOVA; BOCF)	326	−7.6±0.6	329	−8.3±0.6	−0.7 [−2.1; 0.7]	0.313
(ANCOVA; PMI)	326	−10.1±0.5	329	−11.3±0.5	−1.1 [−2.22; −0.04]	0.042
(MMRM; MI)	326	-	329	-	−1.0 [−2.4; 0.3]	0.129
Total alcohol consumption (g/day) (MMRM; OC)	229	−54.1±2.2	212	−59.0±2.9	−4.9 [−10.6; 0.7]	0.088
Total alcohol consumption (g/day)—sensitivity analyses						
(ANCOVA; OC)	229	−56.2±2.5	212	−61.8±2.6	−5.6 [−11.7; 0.5]	0.070
(ANCOVA; LOCF)	326	−51.7±2.2	329	−57.6±2.2	−5.9 [−11.1; −0.7]	0.026
(ANCOVA; BOCF)	326	−37.1±2.8	329	−40.2±2.8	−3.1 [−9.7; 3.5]	0.352
(ANCOVA; PMI)	326	−49.6±2.1	329	−54.8±2.1	−5.2 [−10.2; −0.2]	0.042
(MMRM; MI)	326	-	329	-	−2.9 [−8.5; 2.8]	0.318

SE=Standard error; MMRM=mixed model repeated measures; OC=observed cases; ANCOVA=analysis of covariance; LOCF=last observation carried forward; BOCF=baseline observation carried forward; PMI=placebo mean imputation; MI=multiple imputation.

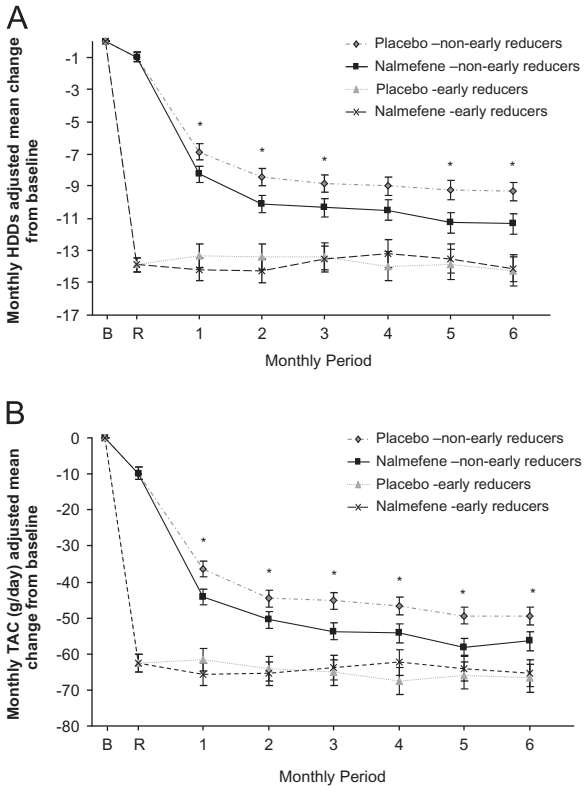

Figure 3 Change in alcohol consumption for patients categorised according to alcohol consumption at randomisation. (A) Adjusted mean change from baseline in monthly heavy drinking days (HDDs). (B) Adjusted mean change from baseline in monthly total alcohol consumption (TAC; g/day). Early reducers=patients having less than 6 HDDs or below medium drinking risk level at randomisation. *$p<0.05$ (difference to placebo), B=baseline, R=randomisation. Bars indicate standard errors.

group, and anxiety, depression, and major depression in the placebo group.

Serious adverse events were reported for 25 patients (including four patients with pre-treatment serious adverse events): 17 patients in the placebo group and 8 patients in the nalmefene group. No serious adverse event was reported in more than one patient in either treatment group, except for intentional overdose (two patients in the placebo group). All the serious adverse events in the nalmefene group, and the majority of serious adverse events in the placebo group were considered not related to study medication by the investigator. There was no pattern in the distribution of serious adverse events across system organ classes, and no indication of specific serious adverse events occurring in the nalmefene group.

Two patients died during the main treatment period: a 50-year-old woman in the placebo group (due to liver disorder as a result of hepatocellular carcinoma) and a 61-year-old man in the nalmefene group (sudden death; unknown cause; assessed by the investigator as being not related to study medication).

One patient in the placebo–placebo group in the run-out period had an intentional overdose of study medication and suicidal behaviour (both serious adverse events). In addition, nine patients were identified with potentially suicide-related adverse events (five on placebo and two on nalmefene in the main treatment period; one in the nalmefene–placebo group in the main treatment and run-out period, and one in the safety follow-up period, after having received placebo); for the majority of these patients, the events were identified as intentional overdoses of the study medication in order to obtain increased efficacy. Fourteen patients (four on placebo, 10 on nalmefene) had one of the selected psychiatric adverse events; none was serious and all the patients fully recovered. In addition one patient had an ongoing selected psychiatric adverse event at baseline. There were no apparent trends in the incidence of potentially clinically significant clinical safety

Table 5 Key secondary analysis (drinking risk level response) at month 6.

Method for handling missing data	Placebo		Nalmefene		Odds ratio	95% CI	*p*-value
	N	Responders (%)	*N*	Responders (%)			
MMRM imputation[a]	326	206 (63%)	329	221 (67%)	1.28	[0.89; 1.83]	0.1833
Sensitivity analyses							
OC	229	156 (68%)	212	150 (71%)	1.24	[0.79; 1.95]	0.357
LOCF	326	207 (63%)	329	219 (67%)	1.24	[0.86; 1.78]	0.248
Non-response	326	156 (48%)	329	150 (46%)	0.92	[0.67; 1.27]	0.630
Sustained response	326	168 (52%)	329	192 (58%)	1.42	[1.02; 2.00]	0.038

OR=odds ratio; CI=confidence interval; drinking risk level response=response defined for patients at very high risk at baseline: as a downward shift to medium risk or below, and for patients at high or medium risk at baseline: as a downward shift to low risk or below; OC=observed cases; LOCF=last observation carried forward; TAC=total alcohol consumption; MMRM=mixed model repeated measures.

[a]Missing values were imputed by response evaluation based on individual patient-predicted values of TAC at each month derived from the MMRM model used in the primary analysis.

laboratory values and no clinically relevant changes over time or differences between the treatment groups were seen in the vital signs, weight, electrocardiogram parameters, or Profile of Mood States total scores.

4. Discussion

This study is the second study in the recently completed clinical phase 3 programme using nalmefene as-needed as a means of reducing alcohol consumption in patients with alcohol dependence. Patients were predominantly middle-aged men, with the majority having a high or very high drinking risk level; the average baseline consumption was 90 g alcohol per day. In line with EMA recommendations, patients with significant withdrawal symptoms were not eligible for participation and thus some of the most severe alcohol dependent patients had to be excluded. The study population is comparable to patients that are likely to present in primary care (Willenbring et al., 2009).

Despite their alcohol problems having started more than 10 years ago, the majority of the patients had never received any treatment. The nalmefene treatment paradigm thus addresses an unmet medical need as it obviously has the potential to engage alcohol dependent patients in treatment who may otherwise not have sought help. Nalmefene does not require the patients to achieve and maintain complete abstinence and the as-needed dosing regimen engages patients with alcohol dependence in active and responsible management of their illness, which may improve patient adherence and persistence to treatment.

The idea of administrating an opioid antagonist (naltrexone) to patients that are still currently drinking, and only when drinking is anticipated (as-needed/targeted use) in order to reduce alcohol consumption has previously been proposed (for review see Sinclair, 2001). As-needed use has been studied with a variety of medications in patients with an alcohol use disorder: nalmefene (Karhuvaara et al., 2007), acamprosate (Laaksonen et al., 2008), disulfiram (Laaksonen et al., 2008), and naltrexone (Heinälä et al., 2001; Kranzler et al., 1997, 2003, 2009; Laaksonen et al., 2008). However, the current study and the recently published study by Mann et al. (2013) are the largest randomised controlled studies of the as-needed use approach with reduction of alcohol consumption as a primary outcome measure in alcohol dependent patients to date.

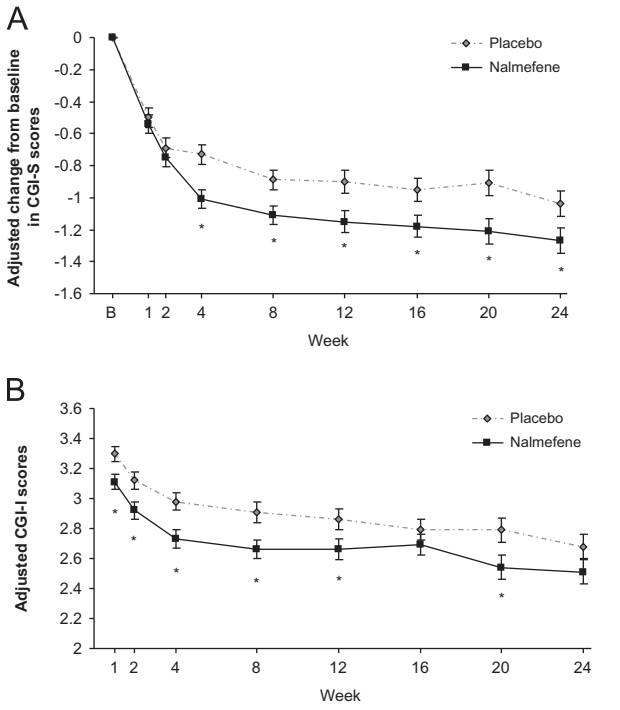

Figure 4 Change in Clinical Global Impression. (A) Adjusted change from baseline in Clinical Global Impression-Severity of Illness (CGI-S) scores. (B) Adjusted Clinical Global Impression-Global Improvement (CGI-I) scores. *$p<0.05$ (difference to placebo), B=baseline. Bars indicate standard errors.

Compared to baseline, there was a substantial reduction in alcohol consumption in both treatment conditions on both co-primary outcome measures: number of heavy drinking days and total alcohol consumption decreased by approximately 65% in the nalmefene group and by

Table 6 Secondary efficacy variables: γ-glutamyltransferase and alanine aminotransferase at week 24.

Efficacy variable	Placebo		Nalmefene		Ratio to placebo		
	N	Mean	*N*	Mean	Ratio	95% CI	*p*-value
γ-glutamyl transferase (IU/L)							
Baseline (geometric mean)	324	52.2	329	52.6			
Adjusted geometric mean at week 24	224	45.0	207	43.4	0.96	[0.86; 1.08]	0.529
Alanine aminotransferase (IU/L)							
Baseline (geometric mean)	324	28.1	329	28.8			
Adjusted geometric mean at week 24	222	27.2	205	25.0	0.92	[0.84; 1.00]	0.049

SD=Standard deviation; CI=confidence interval.

Table 7 Adverse events.

	Placebo (*n*=337)	Nalmefene (*n*=341)
TEAEs[a]	199 (59.1)	232 (68.0)
TEAEs (≥5%)		
Nausea	20 (5.9)	58 (17.0)
Dizziness	15 (4.5)	52 (15.2)
Insomnia	22 (6.5)	49 (14.4)
Headache	26 (7.7)	43 (12.6)
Nasopharyngitis	17 (5.0)	19 (5.6)
Vomiting	8 (2.4)	19 (5.6)
Diarrhoea	17 (5.0)	8 (2.3)
TEAEs leading to dropout[a]	20 (5.9)	23 (6.7)
TEAEs leading to dropout (≥0.5%)[a]		
Dizziness	0 (0.0)	8 (2.3)
Nausea	0 (0.0)	4 (1.2)
Vomiting	0 (0.0)	3 (0.9)
Anxiety	2 (0.6)	2 (0.6)
Insomnia	0 (0.0)	2 (0.6)
Depression	5 (1.5)	1 (0.3)
Major depression	2 (0.6)	0 (0.0)
Serious adverse events[b]	17 (4.7)	8 (2.2)

Data are numbers of patients (%).
TEAE=treatment-emergent adverse event.
[a]In the main treatment period.
[b]In the entire study period; percentages based on the *all-patients-randomised set*.

approximately 60% in the placebo group. Nalmefene was statistically significantly superior to placebo in reducing the number of heavy drinking days at month 6, with a group difference of 1.7 days/month, and also showed a numerically better effect on total alcohol consumption, although non-significantly. The sensitivity analyses were consistently in favour of nalmefene, despite the fact that approaches like placebo mean and multiple imputation minimises the differences between the treatment groups after dropout.

There is no clear-cut answer to what constitutes a clinically relevant magnitude of reduction of heavy drinking. However, the European Medicines Agency's guideline on the development of medicinal products for the treatment of alcohol dependence (European Medicines Agency, 2010) states that efficacy should also be evaluated in terms of the difference in the percentage of treatment responders, e.g. the difference in the percentage of patients with a two-category downshift in the WHO drinking risk levels.

The result of the responder analysis based on a two-category downshift in drinking risk level was consistently numerically in favour of nalmefene, with the exception of the sensitivity analysis that imputed missing values as non-response. However, the non-response imputation can be considered very conservative, with all patients dropping out being considered non-responders, irrespective of the value of total alcohol consumption at the time of dropout; an assumption that is not supported by published data (Project MATCH Research Group, 1998).

The difference between nalmefene and placebo in the number of heavy drinking days per month at month 6 translates into a reduction of about 3 weeks of heavy drinking days per year. From a public health perspective, this difference is relevant, since evidence from epidemiological data have shown that every heavy drinking day carries an increased risk of accidents, aggression, suicide, and cardiac arrest (Rehm et al., 2010). Furthermore, reduction of total alcohol consumption is associated with reduced risk of morbidity and mortality: any reduction in alcohol consumption for a person who consumes more than 10 g of alcohol per day will reduce the annual and life-time risk of alcohol-related death (Rehm et al., 2011).

Efficacy variables independent of the Timeline Follow-back data also provided evidence of the effect of nalmefene. The reduced alcohol consumption was associated with reductions in the liver enzymes GGT and ALAT; the reduction in ALAT was greater in the nalmefene group than in the placebo group. Furthermore, the improvement in the CGI-S scale score, which reflects the global clinical judgement of the severity of illness by an expert clinician, was greater in the nalmefene group than in the placebo group.

The adverse event profile was as expected from published data (Anton et al., 2004; Karhuvaara et al., 2007; Mason et al., 1994, 1999) and reflects the pharmacological profile of nalmefene. There were more patients with serious adverse events in the placebo group compared to the nalmefene group; the incidence of treatment-emergent adverse events leading to dropout was comparable between the groups. Overall, as-needed use of nalmefene was safe and well tolerated and no safety issues were raised in this study.

There are also limitations of this study. The main limitation was the large non-specific treatment response, as evident from the high proportion of patients (approximately 33%) that reduced their drinking prior to start of treatment, before any intervention (medication and BRENDA). At randomisation, these patients consumed such a small amount of alcohol that there was little room for further improvement, irrespective of treatment. This is a phenomenon that has been observed in other alcohol treatment studies, including the recently published study by Mann et al. (2012), and can indeed have an impact on study outcome (Epstein et al., 2005; Litten et al., 2012). No doubt motivational factors (readiness to change), expectancy and natural course could explain why some patients self-initiated a reduction in alcohol consumption immediately after they had been informed about the study and consented to participate and before they started on any treatment intervention. When taking this non-specific treatment response into account, and performing a *post-hoc* analysis of the patients who did not reduce their drinking prior to treatment, the effect of nalmefene was shown to be statistically significant for both co-primary outcome measures, thereby confirming the pharmacological effects of nalmefene relative to placebo in this important subpopulation.

Secondly, the dropout rate in the current study was high, but not very much higher than in another published 6-month study in alcohol dependence (Garbutt et al., 2005) or in studies of a shorter duration (Johnson et al., 2003; Anton et al., 2006). As treatment adherence is a well-known prerequisite for treatment success, nalmefene should only be prescribed in conjunction with continuous psychosocial support, focusing on motivation and treatment adherence.

Thirdly, the results from this study should be interpreted in view of the fact that the study population was limited by the selection criteria, e.g. patients with significant axis I comorbidity were excluded. However, this is directly in line with the European Medicines Agency guideline (European Medicines Agency, 2010).

In conclusion, meeting one of the two predefined co-primary outcome measures in the total population, this study supports the concept of reduction of alcohol consumption with an as-needed use dosing regimen of nalmefene in patients with alcohol dependence that are unable to reduce alcohol intake on their own.

Role of the funding source

The sponsor was involved in the study design, data collection, data analysis, and interpretation of the data, but not in the decision to submit the report for publication. An employee of the sponsor provided medical writing assistance in the preparation of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Contributors

Antoni Gual was the signatory investigator for the study. All authors were involved in the design of the study, data analysis and interpretation. Antoni Gual, Yuan He and Lars Torup wrote the manuscript in collaboration with a medical writer. All authors reviewed and approved the manuscript before submission.

Conflict of interest

Antoni Gual has received honoraria and travel grants from Lundbeck, Janssen, D&A Pharma and Servier.

Yuan He and Lars Torup are Lundbeck employees.

Wim van den Brink has received honoraria from Lundbeck, Merck Serono, Schering-Plough, Reckitt Benckiser, Pfizer, and Eli Lilly, speaker fees from Lundbeck, investigator initiated industry grants from Alkermes, Neurotech, and Eli Lilly, is a consultant to Lundbeck, Merck Serono, Schering-Plough, and Teva, and has performed paid expert testimony for Schering-Plough.

Karl Mann has received research grants from Schering-Plough, Alkermes, Lundbeck, McNeil, and Merck. He has been a paid consultant to Alkermes and Desitin, is a consultant to Lundbeck and Pfizer, and has received speaker fees from Lundbeck.

Acknowledgements

We thank all patients for their participation in the ESENSE 2 Study, all research staff and the ESENSE 2 Study Group (see Supplementary material) for their contributions. We also thank Johan Hellsten, an employee of Lundbeck for providing medical writing assistance in the preparation, revision, and editing of the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2013.02.006.

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