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ORIGINAL ARTICLE

Efficacy of As-Needed Nalmefene in Alcohol-Dependent Patients with at Least a High Drinking Risk Level: Results from a Subgroup Analysis of Two Randomized Controlled 6-Month Studies

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Abstract — Aims: The aim of the study was to investigate the efficacy and safety of as-needed use of nalmefene 18 mg versus placebo in reducing alcohol consumption in patients who did not reduce their alcohol consumption after an initial assessment, i.e. the pooled subgroup of patients with at least a high drinking risk level (men: >60 g/day; women: >40 g/day) at both screening and randomization from the two randomized controlled 6-month studies ESENSE 1 (NCT00811720) and ESENSE 2 (NCT00812461). **Methods:** Nalmefene 18 mg and placebo were taken on an as-needed basis. All the patients also received a motivational and adherence-enhancing intervention (BRENDA). The co-primary outcomes were number of heavy drinking days (HDDs) and mean total alcohol consumption (g/day) in Month 6 measured using the Timeline Follow-back method. Additionally, data on clinical improvement, liver function and safety were collected throughout the study. **Results:** The pooled population consisted of 667 patients: placebo $n = 332$; nalmefene $n = 335$. There was a superior effect of nalmefene compared with placebo in reducing the number of HDDs [treatment difference: −3.2 days (95% CI: −4.8; −1.6); $P < 0.0001$] and total alcohol consumption [treatment difference: −14.3 g/day (−20.8; −7.8); $P < 0.0001$] at Month 6. Improvements in clinical status and liver parameters were greater in the nalmefene group compared with the placebo group. Adverse events and adverse events leading to dropout were more common with nalmefene than placebo. **Conclusion:** As-needed nalmefene was efficacious in reducing alcohol consumption in patients with at least a high drinking risk level at both screening and randomization, and the effect in this subgroup was larger than in the total population.

INTRODUCTION

Nalmefene is an opioid system modulator with antagonist activity at the μ and δ receptors and partial agonist activity at the κ receptor (Bart *et al*., 2005). Nalmefene as-needed has been shown to reduce the total amount of alcohol consumption and number of heavy drinking days (HDDs) and to improve liver function and clinical status in two published 6-month studies in patients with alcohol dependence (Gual *et al*., 2013; Mann *et al*., 2013).

Importantly, a large improvement in both 6-month trials was observed in the first 2 weeks between screening and the start of the treatment: in the Mann *et al*. study, 18% of the patients greatly reduced their alcohol consumption prior to treatment, whereas this was true for 33% of the patients in the Gual *et al*. study. This phenomenon has been reported previously (Epstein *et al*., 2005; Litten *et al*., 2012) and means that a substantial fraction of the patients was treated without a prospect of further improvement. Inclusion of these patients in the pre-specified efficacy analysis may have resulted in a substantial underestimation of the treatment effect. Patients who continued their high level of alcohol consumption after initial assessment and were still drinking at high risk levels at the start of treatment are the patients who are expected to derive the highest clinical benefit from nalmefene, and thus constitute the target population. Nalmefene was recently granted a market authorization in the European Union for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level according to the World Health Organization (WHO, 2000: men: >60 g/day and women: >40 g/day) and who continue to have that 2 weeks after initial assessment (European Medicines Agency, 2013).

This article describes a *post hoc* analysis of the efficacy, safety and tolerability of as-needed nalmefene (18 mg) in the subgroup of patients with at least a high drinking risk level at both screening and randomization, based on the two double-blind, randomized, placebo-controlled 6-month nalmefene efficacy studies: ESENSE 1 (Mann *et al*., 2013; NCT00811720) and ESENSE 2 (Gual *et al*., 2013; NCT00812461).

MATERIALS AND METHODS

Patients

ESENSE 1 was conducted in Germany, Finland, Sweden and Austria (Mann *et al*., 2013), whereas ESENSE 2 was conducted in Belgium, the Czech Republic, France, Italy, Poland, Portugal and Spain (Gual *et al*., 2013). These two 6-month efficacy studies were identical in design. At the screening visit, patient eligibility was evaluated and at the next visit, which occurred 1–2 weeks later, patients were randomized 1:1 to 24 weeks of as-needed treatment with nalmefene or placebo. Eligible patients in each study were men and women aged ≥18 years with a primary diagnosis of alcohol dependence according to the *Diagnostic and Statistical Manual of Mental Disorders* (APA, 2000), assessed with the *Mini-International Neuropsychiatric Interview* (Lecrubier *et al*., 1997). Patients were excluded if they had comorbid psychiatric disorders or an average alcohol consumption below a *medium* drinking risk level (men: ≤40 g alcohol/day; women ≤20 g alcohol/day)

according to the World Health Organization (WHO, 2000). For the full list of selection criteria, see Mann *et al*. (2013) and Gual *et al*. (2013). Both studies were designed and conducted in accordance with the principles of the *Declaration of Helsinki* (WMA, 2008) and *Good Clinical Practice* (ICH, 1996), and each site started patient inclusion only after ethics committee approval. All the patients gave written informed consent.

Randomization and concealment

Eligible patients were assigned to 24 weeks of treatment with as-needed use of either placebo or nalmefene in a 1:1 ratio, according to a computer-generated randomization list (in blocks of 4) provided by the sponsor. 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. Nalmefene and placebo tablets were identical in appearance.

Study procedures

Patients were instructed to take one tablet each day they perceived a risk of drinking alcohol (as-needed dosing), preferably 1–2 h prior to anticipated time of drinking, but otherwise as soon as drinking had started. In addition, all the patients were made to take part in a motivational and adherence-enhancing intervention (BRENDA; Starosta *et al*., 2006) to support them in changing their behaviour and to enhance adherence to treatment, starting at randomization and subsequently at all scheduled visits. No treatment goal was defined, i.e. both abstinence and reduced-risk drinking were accepted; no information on individual treatment goals was collected.

Assessments of efficacy and safety were performed at screening and randomization and Weeks 1, 2 and 4, followed by monthly assessments. Monthly drinking variables were derived from the Time Line Follow-Back (Sobell and Sobell, 1992) used to provide information of daily number of standard drinks. 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 co-primary outcome measures were: change from baseline in the monthly number of HDDs and total alcohol consumption in grams of pure alcohol per day at Month 6. Secondary outcome measures reported here are number of non-drinking days at Month 6, Week 24 Clinical Global Impression-Severity of Illness and Improvement scales [CGI-S and CGI-I (Guy, 1976)], and Week 24 liver function variables, including γ-glutamyltransferase (GGT) and alanine aminotransferase (ALAT).

Safety assessments consisted of evaluation of adverse events, clinical safety laboratory tests, vital signs, weight and electrocardiograms. Adverse events were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA, version 13.0).

Statistical analyses

For the current *post hoc* subgroup analysis, three datasets were used:

The *target population*, comprising all patients with at least a high drinking risk level (men: alcohol consumption >60 g/day; women alcohol consumption >40 g/day), as defined by the World Health Organization (WHO, 2000) at both screening and randomization, was used for the description of the baseline characteristics of the study sample.

The *target safety population*, comprising all patients in the *target population,* but excluding from the dataset those with no recorded study medication intake and all study medication returned, was used for all safety analyses.

The *target efficacy population*, comprising all patients in the *target safety population* with at least one valid post-baseline assessment of HDDs and total alcohol consumption, was used for all efficacy analyses.

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

Efficacy was analysed using mixed model repeated measures (MMRM), using observed cases (OC), with the baseline score as covariate, and country, 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 (see also: Gual *et al*., 2013; Mann *et al*., 2013). To evaluate how different assumptions about missing values would influence the estimate of the treatment effect, sensitivity analyses were performed using analysis of covariance (ANCOVA) by Month 6, using last observation carried forward (LOCF) imputation for missing values and a placebo pattern mixture model in which missing values were imputed using multiple imputation from an MMRM model based on patients in the placebo group with a similar past (Little and Yau, 1996).

CGI-S and CGI-I scores and log-transformed GGT and ALAT values were analysed with similar models as used for MMRM analysis. The CGI-S baseline score was included as a covariate in the model for the CGI-I.

All statistical tests were two-sided and conducted at the 5% level of significance. The statistical software used was SAS®, Version 9.2.

RESULTS

Study sample

The baseline and demographic characteristics of the populations included in the two 6-month efficacy studies (Gual *et al*., 2013; Mann *et al*., 2013) were very similar.

Of the 1322 patients randomized in the two studies, 1320 had a known drinking risk level, and of those, 667 (50.5%) had at least a high drinking risk level (WHO, 2000) at both screening and randomization.

Thus, the *target population* (patients with at least a high drinking risk level both at screening and randomization) comprised 667 patients with 335 patients in the nalmefene group and 332 patients in the placebo group (Table 1).

There were no differences in demographics, alcohol history or other baseline values between the nalmefene and the placebo groups. The mean age at baseline was 48 years, 66% of the patients were men and nearly all of the patients (99%) were Caucasian. The mean BMI at baseline was 26 kg/m^2. The mean age at the onset of problem drinking was 35 years. The majority of patients had not previously been treated for either alcohol dependence (68%) or alcohol withdrawal symptoms (84%) (Table 1).

Table 1. Demographics and baseline clinical characteristics for the total population and for patients with at least a high drinking risk level at both screening and randomization from ESENSE 1 and ESENSE 2 (pooled data)

	Total population (all randomized patients)		High drinking risk level at screening and randomization (target population)	
	Placebo (658)	Nalmefene (664)	Placebo (332)	Nalmefene (335)
Race				
Caucasian	654 (99.4%)	659 (99.2%)	329 (99.1%)	333 (99.4%)
Sex				
Men	458 (69.6%)	470 (70.8%)	216 (65.1%)	223 (66.6%)
Age (years)	47.9 (10.7)	47.8 (10.8)	48.7 (10.5)	48.4 (10.5)
Body Mass Index, kg/m^2	25.8 (4.3)	25.8 (4.5)	26.1 (4.4)	26.0 (4.8)
Age at onset of problem drinking	34.5 (11.9)	35.0 (12.2)	35.1 (11.6)	35.6 (12.3)
Total monthly HDDs (days)	18.9 (7.0)	19.6 (7.1)	22.4 (6.0)	22.9 (5.9)
Total alcohol consumption (g/day)	86.7 (45.3)	88.8 (44.8)	103.3 (44.5)	107.7 (45.5)
Clinical Global Impression – Severity of Illness	4.0 (1.5)	4.0 (1.5)	4.3 (1.4)	4.3 (1.4)
γ-Glutamyltransferase (IU/l)[a]	52.8	51.8	57.6	55.8
Alanine aminotransferase (IU/l)[a]	28.5	28.9	29.1	29.5
Mean corpuscular volume (fl)[a]	97.2	97.4	97.4	97.7
Carbohydrate-deficient transferrin (%)	2.5 (1.3)	2.6 (1.5)	2.6 (1.5)	2.8 (1.7)
Drinker inventory of consequences total score	41.0 (21.7)	41.7 (22.3)	42.2 (22.2)	41.1 (22.3)
Alcohol dependence scale total score	13.5 (5.7)	13.8 (5.8)	13.3 (5.7)	14.0 (6.0)
Current smoker				
Yes	391 (59.4%)	383 (57.7)	192 (57.8%)	184 (54.9%)
Living alone				
Yes	187 (28.4%)	187 (28.2%)	99 (29.8%)	88 (26.3%)
Unemployed				
Yes	151 (22.9%)	139 (20.9%)	82 (24.7%)	83 (24.8%)
Previously treated for alcohol dependence				
Yes	236 (35.9%)	233 (35.1%)	112 (33.7%)	105 (31.3%)
Previously treated for alcohol withdrawal symptoms				
Yes	121 (18.4%)	117 (17.6%)	59 (17.8%)	49 (14.6%)
Family history of alcohol problem				
Yes	381 (57.9%)	406 (61.1%)	209 (63.0%)	211 (63.0%)

Data are mean (SD) or number of patients (%).
SD, standard deviation.
[a]Geometric mean.

There were no differences in demographics, alcohol history or other baseline values between the nalmefene and placebo group in the *target population.* The demographic characteristics and treatment history of the *target population* were very similar to those of the patients not eligible for this *post hoc* subgroup analysis (complementary subgroup) and to those of the total population. However, the *target population* had a higher mean number of HDDs and a higher total alcohol consumption, a slightly higher mean CGI-S score and a slightly higher GGT level at baseline (Table 1 and Supplementary material, Table S1).

Nine patients in the *target population* did not take study medication and were thus not included in the *target safety population* used for the safety evaluation. In addition, 17 patients in the *target safety population* did not have a valid post-baseline efficacy assessment; the *target efficacy population* therefore comprised 641 patients, 322 in the placebo group and 319 in the nalmefene group (Fig. 1).

In the *target safety population*, the completion rates in ESENSE 1 were 63.3% for placebo and 43.0% for nalmefene, whereas in ESENSE 2 completion rates were 63.9% for placebo and 63.8% for nalmefene. In ESENSE 1, the adverse event dropout rate was higher for nalmefene (25.1%) compared with placebo (7.7%), whereas in ESENSE 2, the dropout rates were similar for the placebo (3.8%) and nalmefene (3.3%) groups (Fig. 1).

On average, patients on placebo took study medication on 72% of the days in the main treatment period, whereas patients on nalmefene took study medication on 58% of the days (Table 2).

Efficacy

Heavy drinking days

At baseline, the mean number of HDDs in ESENSE 1 was 23.1 days/month (placebo) and 23.0 days/month (nalmefene), whereas in ESENSE 2 this was 21.6 days/month (placebo) and 22.7 days/month (nalmefene) (ESENSE 2). For patients who provided efficacy data at Month 6, the number of HDDs at Month 6 in ESENSE 1 was 14.0 days/month (placebo) and 9.3 days/month (nalmefene), whereas in ESENSE 2 this was 12.0 days/month (placebo) and 10.0 days/month (nalmefene). The MMRM analysis showed that as-needed nalmefene was statistically significantly better than placebo in reducing the number of HDDs from Month 1 onwards in both ESENSE 1 and ESENSE 2 (Supplementary material, Fig. S1): at Month 6, the estimated mean change from baseline in HDD [± standard error (SE)] for ESENSE 1 was −8.0 ± 1.0 days/month for the placebo group and −11.6 ± 1.0 days/month for the nalmefene group, corresponding to a treatment effect of −3.7 HDDs/month (95% CI: −5.9 to −1.5, $P = 0.0010$) in favour of nalmefene. For ESENSE 2, the estimated mean change from

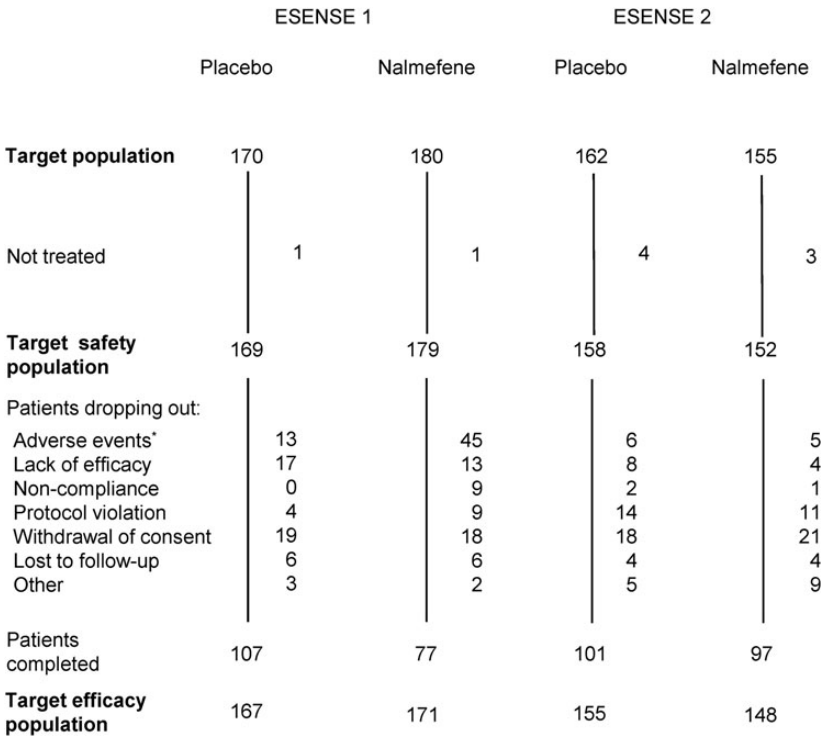

Fig. 1. Flow chart of patient disposition. *Adverse events were not by default set to primary reason for dropout.

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	323	Mean	72.3
		Median	76.2
		10th percentile	38.6
		90th percentile	98.8
Nalmefene	326	Mean	57.8
		Median	59.2
		10th percentile	13.6
		90th percentile	97.1

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

baseline in HDD at Month 6 was −10.2 ± 0.9 days/month for the placebo group and −12.9 ± 0.9 days/month for the nalmefene group, corresponding to a treatment effect of −2.7 HDDs/month (95% CI: −5.0 to −0.3, $P = 0.0253$) in favour of nalmefene.

In the two studies, the standardized effect sizes (Cohen's *d*) for the number of HDDs were 0.37 for ESENSE 1 and 0.27 for ESENSE 2.

For the pooled *target population* (Fig. 2A), the estimated mean change from baseline in HDD at Month 6 was −9.4 ± 0.7 days/month for the placebo group and −12.6 ± 0.7 days/month for the nalmefene group, corresponding to a treatment effect of −3.2 HDDs/month (95% CI: −4.8 to −1.6, $P < 0.0001$) in favour of nalmefene with a standardized effect size (Cohen's *d*) of 0.33. In comparison, for the pooled total population from ESENSE 1 and 2 (i.e. including patients below high drinking risk level at screening or randomization), the treatment effect was −2.0 HDDs/month (95% CI: −3.0 to −1.0, $P < 0.0001$) in favour of nalmefene with a standardized effect size (Cohen's *d*) of 0.26. The complementary subgroup (i.e. patients below high drinking risk level at screening or randomization) substantially reduced the number of HDDs from screening to randomization, with only a minor reduction from randomization to Month 6 and no differences between the treatment groups (Supplementary material, Fig. S2).

For both studies (separately and pooled), the sensitivity analyses, based on different imputation methods for missing data, were consistently in favour of nalmefene (Supplementary material, Fig. S3).

Total alcohol consumption

Results similar to those obtained for HDDs were observed for the change from baseline in total alcohol consumption. Mean baseline values in ESENSE 1 were 99 g/day (placebo) and 102 g/day (nalmefene) and 108 g/day (placebo) and 114 g/day (nalmefene) in ESENSE 2. For patients who provided efficacy data at Month 6, in ESENSE 1 the mean total alcohol consumption at Month 6 was 57.0 g/day (placebo) and 39.6 g/day (nalmefene) and in ESENSE 2 this was 51.6 g/day (placebo) and 44.0 g/day (nalmefene). The MMRM analysis showed that as-needed nalmefene was statistically significantly better than placebo in reducing the mean total alcohol consumption from Month 1 onwards in both ESENSE 1 and ESENSE 2 (Supplementary material, Fig. S4): at Month 6, the estimated mean change from baseline in total alcohol consumption for ESENSE 1 was −40.0 ± 3.9 g/day for the placebo group and −58.3 ± 4.1 g/day for the nalmefene group, corresponding to a treatment effect of −18.3 g/day (95% CI: −26.9 to −9.7, $P < 0.0001$) in favour of nalmefene, whereas

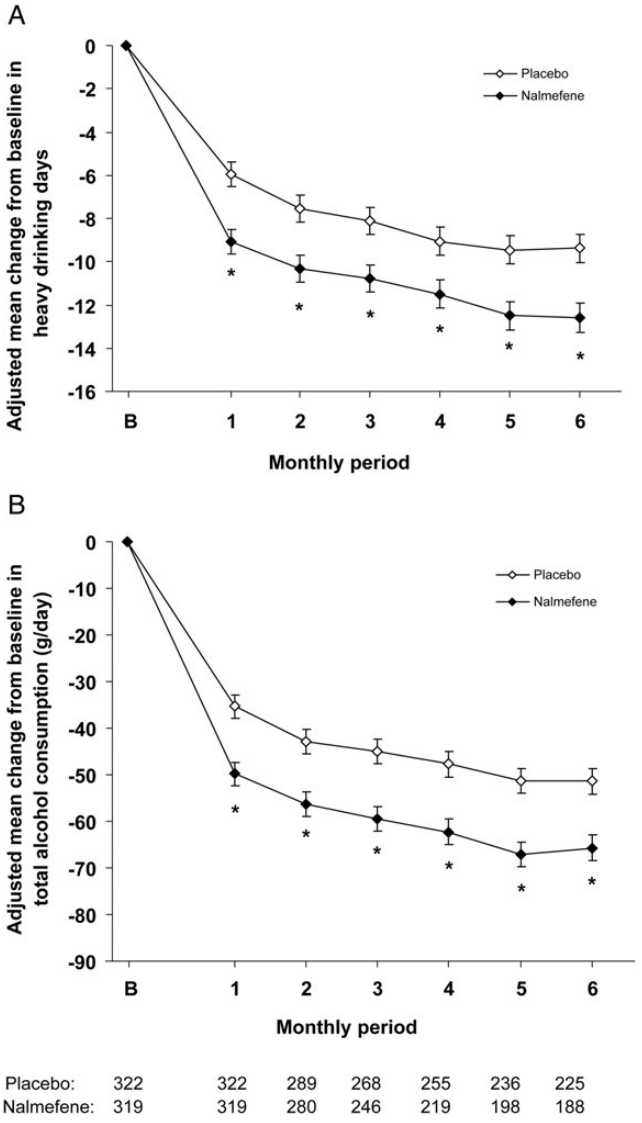

Fig. 2. Monthly adjusted mean change from baseline in (**A**) heavy drinking days and (**B**) total alcohol consumption for patients with high drinking risk level at screening (i.e. baseline) and randomization from ESENSE 1 and ESENSE 2 pooled. Numbers below the x-axis indicate number of patients contributing with observations at each month. *$P < 0.05$ compared to placebo. Values are means ± the standard error (SE). B = baseline.

for ESENSE 2, the estimated mean change from baseline in total alcohol consumption at Month 6 was −60.1 ± 4.0 g/day for the placebo group and −70.4 ± 4.0 g/day for the nalmefene group, corresponding to a treatment effect of −10.3 g/day (95% CI: −20.2 to −0.5, $P = 0.0404$) in favour of nalmefene.

In the two studies, the standardized effect sizes (Cohen's *d*) for total alcohol consumption were 0.46 and 0.25, respectively.

For the pooled *target population* (Fig. 2B), the estimated mean change from baseline in total alcohol consumption at Month 6 was −51.4 ± 2.8 g/day for the placebo group and −65.7 ± 2.8 g/day for the nalmefene group, corresponding to a treatment effect of −14.3 g/day (95% CI: −20.8 to −7.8, $P < 0.0001$) in favour of nalmefene with a standardized effect size of 0.36. In comparison, for the pooled total population from ESENSE 1 and 2 (i.e. including patients below high risk-drinking level at screening or randomization), there was a treatment effect of −7.6 g/day (95% CI: −11.6 to −3.5, $P = 0.0003$) in favour of nalmefene with a standardized effect size (Cohen's *d*) of 0.23. The complementary subgroup (i.e. patients below high drinking risk level at screening or randomization) substantially reduced the total alcohol consumption from screening to randomization, with only a minor reduction from randomization to Month 6 and no differences between the treatment groups (Supplementary material, Fig. S2).

For both studies (separately and pooled), the sensitivity analyses, based on different imputation methods for missing data, were consistently in favour of nalmefene (Supplementary material, Fig. S5).

Secondary outcomes

At baseline, the mean number of non-drinking days (standard deviation) was 3.6 ± 5.0 in the placebo group and 3.5 ± 5.1 in the nalmefene group for the pooled *target population*. The mean number of non-drinking days increased to 9.3 ± 9.6 in the placebo group and to 10.9 ± 9.8 in the nalmefene group at Month 6. The geometric mean GGT values decreased more from baseline to Week 24 in the nalmefene group than in the placebo group with a ratio of 0.73 ($P < 0.05$) in favour of nalmefene in ESENSE 1 and a ratio of 0.90 numerically in favour of nalmefene in ESENSE 2 (Table 3). Similar results were obtained for ALAT with ratio's of 0.83 and 0.85 ($P < 0.05$) in favour of nalmefene in ESENSE 1 and ESENSE 2, respectively.

The clinical relevance of the reductions in HDD and total alcohol consumption was also shown by the improvements in the CGI scores. In ESENSE 1 (Fig. 3), the adjusted mean change in the CGI-S score (± SE) was −0.7 ± 0.1 for placebo and −1.1 ± 0.1 for nalmefene, corresponding to a treatment effect of −0.4 (95% CI: −0.7 to −0.1; $P = 0.0051$) in favour of nalmefene. In ESENSE 2 (Fig. 3), the adjusted mean change in the CGI-S score was −0.9 ± 0.1 for placebo and −1.3 ± 0.1 for nalmefene, corresponding to a treatment effect of −0.5 (95% CI: −0.8 to −0.1; $P = 0.0050$) in favour of nalmefene.

There were also significant differences in favour of nalmefene in the CGI-I in both studies (Fig. 4): significant differences to placebo of −0.6 (ESENSE 1) and −0.3 (ESENSE 2) in the adjusted mean CGI-I scores.

Safety and tolerability

The safety profile of nalmefene in patients with at least a high drinking risk level both at screening and randomization was similar to that observed in the total population (Gual *et al*., 2013; Mann *et al*., 2013). During the 6-month treatment period, ~77% of patients in the nalmefene group had one or more adverse events, and the most commonly reported adverse events were dizziness, nausea and insomnia (Table 4).

The adverse events with the highest incidences were central nervous system and gastrointestinal events, which had higher incidences in the nalmefene group than in the placebo group and reflect antagonism by nalmefene at opioid receptors. The majority of these adverse events were transient (3–7 days), occurring within 1 day of the first dose, and were mild or moderate in intensity. During the treatment period, 26 (8.0%) placebo and 58 (17.5%) nalmefene patients dropped out due to adverse events (Table 4). Treatment-emergent adverse events leading to dropout in ≥5 patients in either treatment

Table 3. Liver enzymes γ-glutamyltransferase and alanine aminotransferase at Week 24 in patients with at least a high drinking risk level at both screening and randomization in ESENSE 1 and ESENSE 2

	Placebo		Nalmefene		Ratio to placebo		
Efficacy variable	*n*	Mean	*n*	Mean	Ratio	95% CI	*P*-value
ESENSE 1							
γ-Glutamyl transferase (IU/l)							
Baseline (geometric mean)	167	60.1	171	55.7			
Adjusted geometric mean at Week 24	112	53.9	87	39.5	0.73	(0.64; 0.84)	<0.001
Alanine aminotransferase (IU/l)							
Baseline (geometric mean)	166	29.3	171	29.4			
Adjusted geometric mean at Week 24	110	29.6	87	24.7	0.83	(0.75; 0.93)	0.001
ESENSE 2							
γ-Glutamyl transferase (IU/l)							
Baseline (geometric mean)	153	54.9	148	55.9			
Adjusted geometric mean at Week 24	108	52.4	100	47.3	0.90	(0.76; 1.07)	0. 244
Alanine aminotransferase (IU/l)							
Baseline (geometric mean)	153	29.0	148	29.3			
Adjusted geometric mean at Week 24	108	31.5	100	26.8	0.85	(0.75; 0.96)	0.010

SD, standard deviation; CI, confidence interval.

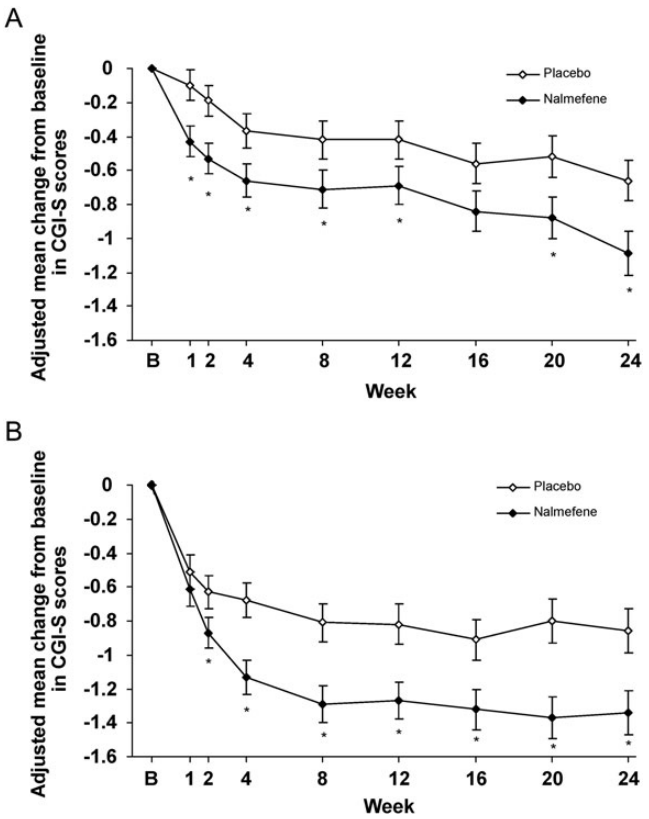

Fig. 3. Change in clinical global impression-severity of illness. Adjusted mean change from baseline in Clinical Global Impression-Severity of Illness (CGI-S) scores for patients with at least a high drinking risk level at screening and randomization in (**A**) ESENSE 1 and (**B**) ESENSE 2. Values are means ± the standard error (SE). *$P < 0.05$ compared with placebo. B, baseline.

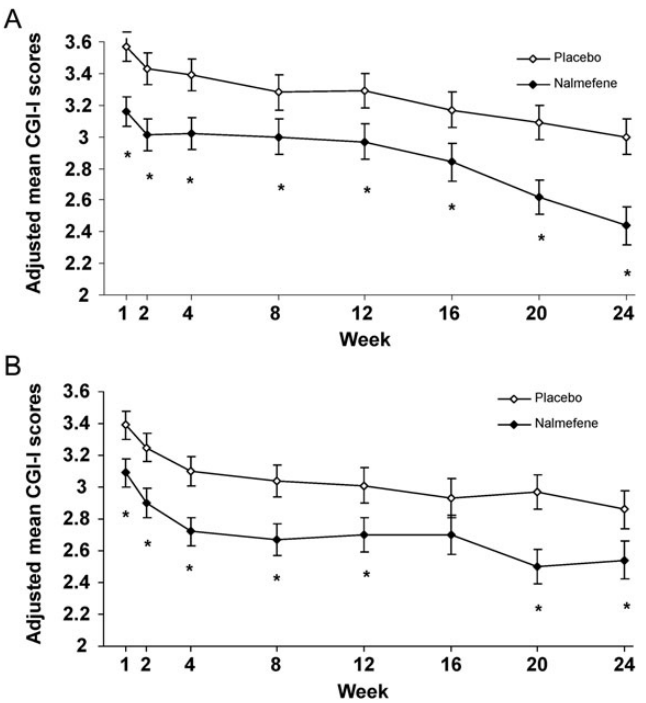

Fig. 4. Change in clinical global impression-global improvement. Adjusted mean Clinical Global Impression-Global Improvement (CGI-I) scores for patients with at least a high drinking risk level at screening and randomization in (**A**) ESENSE 1 and (**B**) ESENSE 2. Values are means ± the standard error (SE). *$P < 0.05$ compared with placebo.

group were dizziness ($n = 18$), nausea ($n = 16$), headache ($n = 8$), fatigue ($n = 5$) and sleep disorder ($n = 5$) in the nalmefene group.

Serious adverse events were reported by 12 placebo patients (3.7%) and 15 nalmefene patients (4.5%). There were no serious adverse events that were reported by more than one patient in either treatment group. Serious adverse events led to the dropout of six placebo patients (1.8%) and five nalmefene patients (1.5%). No deaths occurred.

DISCUSSION

In the 6-month nalmefene trials (Gual *et al*., 2013; Mann *et al*., 2013), a substantial number of the patients reduced their drinking considerably in the period between screening and

Table 4. Adverse events in the *target safety population* ($n = 658$)

Preferred term	Placebo, $n = 327$	Nalmefene, $n = 331$
Patients with treatment-emergent adverse events	220 (67.3%)	256 (77.3%)
Treatment-emergent adverse events (≥5%):		
Dizziness	21 (6.4%)	78 (23.6%)
Nausea	23 (7.0%)	78 (23.6%)
Insomnia	15 (4.6%)	49 (14.8%)
Headache	33 (10.1%)	46 (13.9%)
Fatigue	20 (6.1%)	34 (10.3%)
Sleep disorder	2 (0.6%)	28 (8.5%)
Nasopharyngitis	36 (11.0%)	26 (7.9%)
Vomiting	12 (3.7%)	25 (7.6%)
Decreased appetite	4 (1.2%)	19 (5.7%)
Hyperhidrosis	3 (0.9%)	18 (5.4%)
Diarrhoea	21 (6.4%)	12 (3.6%)
Accidental overdose[a]	18 (5.5%)	8 (2.4%)
Patients with treatment-emergent adverse events leading to dropout	26 (8.0%)	58 (17.5%)
Treatment-emergent adverse events leading to dropout of ≥5 patients in either treatment group:		
Dizziness	0 (0.0%)	18 (5.4%)
Nausea	0 (0.0%)	16 (4.8%)
Headache	0 (0.0%)	8 (2.4%)
Fatigue	0 (0.0%)	5 (1.5%)
Sleep disorder	0 (0.0%)	5 (1.5%)

Data are numbers of patients (%).
[a]Defined as >1 tablet of study medication.

randomization, i.e. prior to receiving any treatment; the vast majority of those patients (87% in the nalmefene group and 92% in the placebo group) maintained low drinking levels till the end of the study (Gual *et al*., 2013). These patients may represent excessive drinkers who after making the decision to seek help can reduce their drinking with minimal intervention. That such a population exists is well known (Beich *et al.*, 2003). Taking this phenomenon into account, a *post hoc* analysis of the treatment effects in the subgroup of alcohol-dependent patients with at least a high dinking risk level both at screening and at randomization was performed.

Patients in the target population were very similar to those in the total population in terms of sociodemographic variables, but the target population reported more HDDs and a higher total alcohol consumption levels than the total study population: 22.4 versus 19.3 HDDs/month and 105.5 versus 87.7 g/day. Liver function indicators were marginally different. Similar to the total population, only a third of the target population had been in previous treatment for alcohol dependence.

The magnitude of the treatment effect was larger in the target population than in the total treatment population in both trials separately and in the pooled data of both trials: difference in reduction in HDD −3.2/month (Cohen's $d = 0.33$) versus −2.0/month (Cohen's $d = 0.26$) and difference in reduction in total alcohol consumption −14.3 g/day (Cohen's $d = 0.36$) versus −7.6 g/day (Cohen's $d = 0.23$) in the target population and the total population, respectively. These effect sizes are larger than those reported for heavy drinking outcomes in licensed medications for abstinence in alcohol dependence and within the range reported for approved medicinal products in other central nervous system indications (Leucht *et al*., 2012; Maisel *et al*., 2013). The robustness of the effect of nalmefene on HDDs and total alcohol consumption was confirmed by the various sensitivity analyses.

As in the total population, there were larger improvements in the liver function parameters (GGT and ALAT) and clinical global impression scores in the nalmefene group compared with the placebo group (Gual *et al*., 2013; Mann *et al*., 2013).

The safety profile of nalmefene in the target population was very similar to the one observed in the total population and the incidence of serious adverse events was similar in placebo patients (3.7%) and nalmefene patients (4.5%).

It is well known that an assessment of recent drinking and drinking-related problems can have profound effects on drinking behaviour in people with alcohol use problems (Kaner *et al*., 2009; McQueen *et al*., 2011). Most patients in the 6-month studies had no previous treatment experience and stepped care approaches starting with a brief intervention (including an assessment of the current problems) are likely to fit the treatment needs of such a population (Sobell and Sobell, 2000; Drummond *et al*., 2009). In addition, all patients received a motivational and adherence-enhancing intervention (BRENDA) and this intervention may have had a substantial effect in this largely treatment-naïve patient population (Kaner *et al*., 2009). It is therefore not surprising that the response in the placebo group was relatively high, similar to what has been shown in other studies in patients with alcohol dependence (e.g. Johnson *et al*., 2003; Mann *et al*., 2012). The statistically significant and clinically relevant effect of nalmefene should be valued against this background.

This study has limitations. Firstly, the results from this analysis should be interpreted in view of the fact that the original study population was limited by the selection criteria, e.g. patients with significant axis I co-morbidity and serious withdrawal symptoms were excluded. However, this is directly in line with the European Medicines Agency guideline (European Medicines Agency, 2010). Secondly, the analyses of the target population were performed *post hoc*. However, targeting the population who did not reduce their alcohol consumption after an initial period of observation (1–2 weeks in the clinical studies) is highly clinically relevant, given that a two-step approach for patients unable to change their behaviour after initial counselling is typically used in clinical practice across many different disease areas. This supports the external validity of the selection of the target population. Thirdly, this *post hoc* analysis is not based on the total randomized population. However, the selection of the target population is based on patient behaviour that occurred before randomization. Moreover, the number of nalmefene and placebo patients was very similar and there were no differences in demographics, alcohol history or other baseline characteristics that we measured between the nalmefene and placebo group in the target population, making selection bias and confounding highly unlikely and supporting the internal validity.

Based on this *post hoc* analysis, we conclude that nalmefene as-needed should be offered to those alcohol-dependent patients in primary care and outpatient addiction treatment services who are not able to reduce their alcohol consumption following an initial assessment or brief intervention (Kaner *et al*., 2009; McQueen *et al*., 2011). We also conclude that full abstinence is not the only acceptable treatment goal, but patients and therapists can choose between abstinence and reduced-risk drinking based on the patient's condition and

preference (Hodgins *et al*., 1997; Heather *et al*, 2010) and that shared decision making on treatment goal and treatment strategy may result in lower dropout and higher adherence rates (Joosten *et al*., 2008; Perestelo-Perez *et al*., 2011).

Introduction of pharmacologically supported reduced-risk drinking interventions may ultimately narrow the unacceptable treatment gap with currently only a small percentage of the alcohol-dependent population in some state-of-the-art treatment (Alonso *et al*., 2004; Cohen *et al*., 2007).

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Alcohol and Alcoholism* online.

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