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Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study

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Abstract

This study evaluated the long-term efficacy and safety of nalmefene treatment in reducing alcohol consumption. We randomised (1:3) 675 alcohol-dependent patients ≥ 18 years of age to 52 weeks of as-needed treatment with placebo or nalmefene 18 mg/day: A total of 112 patients (68%) in the placebo group and 310 (62%) in the nalmefene group completed the study. At month 6, the co-primary outcome variables showed no statistically-significant differences between the treatment groups; but at month 13, nalmefene was more effective than placebo, both in the reduction of the number of heavy drinking days (HDDs) (-1.6 days/month (95% CI $-2.9; -0.3$); $p = 0.017$) and the reduction of total alcohol consumption (TAC) (-6.5 g/day last month (95% CI $-12.5; -0.4$); $p = 0.036$). In a subgroup analysis of patients with high/very high drinking risk levels at screening and at randomisation (the *target population*), there was a significant effect in favour of nalmefene on TAC at month 6, and on both HDD and TAC at month 13. Improvements in Clinical Global Impression and liver enzymes were greater with nalmefene, compared to placebo. Most adverse events were mild or moderate, and transient; adverse events, including those leading to dropout, were more common with nalmefene. This study provides evidence for the long-term safety and efficacy of nalmefene as-needed in alcohol-dependent patients whom continue to drink heavily, following a brief intervention.

Keywords

Addiction, adverse effects, alcohol dependence, alcoholism, as-needed therapy, Clinical Global Impression, harm reduction, liver enzymes, nalmefene

This study is registered at ClinicalTrials.gov, NCT 00811941

Introduction

With almost 15 million affected persons in the European Union (EU) and 8 million affected persons in the USA, alcohol dependence is a worldwide major public health problem (Anton et al., 2006; Wittchen et al., 2010); however, in the EU, less than 10% of the people with alcohol dependence receive any treatment (Alonso et al., 2004) and the corresponding figure for the USA is approximately 25% (Kohn et al., 2004). Possible reasons for this unfortunate situation include the perceived stigmatisation associated with seeking treatment (Keyes et al., 2010), the limited abstinence rates of patients after alcohol dependence treatment (Anton et al., 2006; Mann et al., 2004; Merckx et al., 2011; Miller et al., 2001) and the related negative image of addiction treatment services (Nabitz et al., 2006); and finally, the unwillingness of many alcohol-dependent people to engage in abstinence-oriented treatment (Gastfriend et al., 2007; Marlatt and Witkiewitz, 2002) and their preference for treatments that are directed at reduced drinking (Heather et al., 2010; Hodgins et al., 1997). Allowing patients to choose between abstinence and reduced drinking as their treatment goal may, therefore, enhance engagement with the treatment, ultimately leading to better outcomes for individual people and the population at large (Adamson et al., 2010; Heather et al., 2010;). Based on these considerations and preliminary

findings of its feasibility and effectiveness (van Amsterdam and van den Brink, 2013), reduced drinking is increasingly accepted as a viable treatment goal by professionals and official agencies (European Medicines Agency, 2010; Klingemann and Rosenberg, 2009; Luquiens et al., 2012; Rosenberg et al., 1996).

Recently we have shown, in two 6-month trials in patients with alcohol dependence, that as-needed use of the opioid system modulator nalmefene is effective, well-tolerated and safe in the reduction of total alcohol consumption and the number of

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heavy drinking days, resulting in clinically-relevant increases in the percentage of responders, clinician-rated improvements and liver function (Gual et al., 2013; Mann et al., 2013). In addition, we have shown that patients with high or very high drinking risk levels (according to the World Health Organisation (WHO, 2000): men whom drink > 60 g/day and women, > 40 g/day) at screening and at randomisation benefit more from nalmefene than patients with lower or less stable heavy drinking levels (van den Brink et al., 2013). Based on these findings, nalmefene was recently granted a market authorisation in the EU for the reduction of alcohol consumption in adult patients with alcohol dependence and a continued high drinking risk level 2 weeks after an initial assessment (European Medicines Agency, 2013).

The current study investigates the long-term efficacy, tolerability and safety of nalmefene in the treatment of alcohol-dependent patients, with analyses for:

- (a) The total study population; and
- (b) The subgroup with high or very high drinking risk levels at the start of treatment.

Methods and materials

Patients

This randomised, double-blind, placebo-controlled, parallel-group study included patients enrolled at 60 sites in the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Russia, Slovakia, Ukraine and the UK. Patients were recruited from outpatient clinics, from the study sites' own patient pool, by referrals to the study site, or by using advertisements.

Eligible patients were men and women aged ≥ 18 years with a primary diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR™) (American Psychiatric Association, 2000), as assessed with the Mini-International Neuropsychiatric Interview (Lecrubier et al., 1997), and having a blood alcohol concentration < 0.02% at the screening visit.

Exclusion criteria were:

1. Less than six heavy drinking days (European Medicines Agency, 2010), defined as a day with alcohol consumption ≥ 60 g for men and ≥ 40 g for women; or more than 14 consecutive abstinent days in the 4 weeks preceding screening;
2. A Revised Clinical Institute Withdrawal Assessment for Alcohol (Sullivan et al., 1989) score ≥ 10 (indicating the need for medication-supported detoxification);
3. Aspartate aminotransferase (ASAT) and/or alanine aminotransferase (ALAT) values more than 3 times of upper normal limit; or
4. 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 each site started

patient inclusion only after ethics committee approval. All patients gave written informed consent.

Randomisation and masking

At baseline (week 0), eligible patients were assigned to 52 weeks of treatment with as-needed use of either placebo or nalmefene 18 mg (base) in a 1:3 ratio, according to a computer-generated randomisation list (in blocks of 4), provided by the sponsor. The 3:1 ratio was chosen to have at least 100 patients treated with nalmefene for at least 1 year, for the study of long-term safety. 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 nalmefene and placebo tablets were identical in appearance.

Procedures

The study consisted of a 1–2 week screening period, followed by a 52-week double-blind treatment period with either nalmefene or placebo. A safety follow-up was scheduled for 4 weeks after study completion or withdrawal.

Patients were instructed to take one tablet on each day they perceived a risk of drinking alcohol (as-needed dosing), preferably 1–2 hours before 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. We used the Timeline Follow-back Procedure (Sobell and Sobell, 1992) to obtain estimates of daily drinking, as well as to record medication intake. In addition, all patients took part in a motivational and adherence-enhancing intervention called BRENDA (Starosta et al., 2006; Volpicelli et al., 2001) to support them in changing their behaviour and to enhance adherence to treatment, starting at randomisation and subsequently, at all scheduled visits. Both abstinence and reduction were acceptable treatment goals.

Assessments of efficacy and safety measures were performed at screening (week 1–2); randomisation; and weeks 1, 2 and 4; followed by monthly assessments. For a full description of the timing of assessments, see the supplementary material.

Monthly drinking variables were derived from the Timeline Follow-back Procedure (Sobell and Sobell, 1992), which provided information about the 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: United Kingdom, 8 g; Hungary, Latvia and Poland, 10 g; Estonia, Lithuania, Russia, Slovakia and Ukraine, 14 g; and Czech Republic, 16 g. At screening, patients reported their daily drinking over the previous month. At subsequent visits, they reported drinking since the previous visit.

The pre-defined co-primary outcome measures were the change from baseline in heavy drinking days and the total alcohol consumption (g/day) at 6 months after study initiation. The pre-defined key-secondary outcome measure was the drinking risk level response (change 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 the 6-month time point.

Other secondary outcome measures included drinking outcomes at month 13 (i.e. at the end of 1 year of treatment; if 1 month is 28 days), clinician-based judgments using the Clinical Global Impression - Severity of Illness (CGI-S) and the Global Improvement (CGI-I) scales (Guy, 1976), alcohol dependence severity based on the Alcohol Dependence Scale (Skinner and Horn, 1984), the consequences of excessive alcohol use based on the Drinker Inventory of Consequences (Miller et al., 1995), and liver functions such as γ -glutamyltransferase (GGT) and ALAT.

Secondary outcome measures reported here are the 13-month drinking outcomes; the 6-month CGI-S and CGI-I scores; and the GGT, ALAT and % carbohydrate-deficient transferrin (CDT) values. We will report other secondary variables elsewhere. For the full list of outcome variables, see the supplementary material.

Safety assessments consisted of evaluation of adverse events (including pre-treatment and treatment-emergent (i.e. occurring at or after the first dose) adverse events), clinical safety laboratory tests, vital signs, weight, electrocardiograms, and Profile of Mood States (POMS) (McNair et al., 1971).

To capture any signal related to psychiatric adverse events, a group of selected preferred terms was pre-defined (see supplementary material). We identified adverse events potentially related to suicide using the sub-standardised Medical Dictionary for Regulatory Activities query 'suicide/self-injury'. We coded adverse events using the lowest-level term from the Medical Dictionary for Regulatory Activities, Version 13.0.

Statistical analysis

The sample size calculation was based on a standard deviation (SD) for the change from baseline in number of heavy drinking days of 7 days and the change from baseline in total alcohol consumption of 36.5g/day and a correlation of 0.7 between heavy drinking days and total alcohol consumption. With a significance level of 5%, 668 patients randomised in a 3:1 ratio would provide a power of 90% for detecting a difference between the treatment groups of three heavy drinking days and 12 g/day in total alcohol consumption, accounting for an expected drop-out rate of 20% by 6 months. In the event that up to 15% of the patients would be excluded from the *full-analysis set* because of being in the WHO low drinking risk level category at baseline, the power would still be preserved at 85%.

Three datasets were pre-specified in the study protocol:

1. The *all-patients-randomised set*, comprising all randomised patients.
2. 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 safety analyses.
3. The *full-analysis set*, comprising all patients in the *all-patients-treated set* with at least one valid post-baseline assessment of alcohol consumption and an average alcohol consumption at medium risk or above, according to WHO criteria (> 40 g/day for men and > 20 g/day for women), was used for all pre-defined efficacy analyses.

The baseline for drinking variables was defined as the 28 days 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 a mixed model repeated measures model, using observed cases, with the baseline score as covariate and site, sex, time (months 1 to 13) and treatment as fixed effects; the baseline score-by-time and treatment-by-time interactions were also included in the model.

Sensitivity analyses were performed using analysis of covariance (ANCOVA) by month, with the same covariates and fixed effects as in the mixed model repeated measures analysis, using observed cases, last observation carried forward and baseline observation carried forward imputation for missing values. In addition, a post-hoc sensitivity ANCOVA, with missing values imputed by the month 1 estimation in the placebo group, was performed.

The null hypothesis of no difference in treatment effect on the co-primary outcome variables (heavy drinking days and total alcohol consumption) had to be rejected in order to proceed with formal testing of the key-secondary outcome measure, drinking risk level response at month 6; which was analysed by logistic regression with country, sex, baseline drinking risk level and treatment as fixed effects, imputing missing values based on individual patient-predicted values of total alcohol consumption derived from the mixed model repeated measures analysis. The odds ratio (OR) of nalmefene compared to placebo, with a 95% confidence interval (CI) and corresponding *p*-value, based on the likelihood ratio test, was estimated from the model.

The other secondary outcome measures (drinking outcomes at 13 months, CGI-S and CGI-I scores, %CDT, and log-transformed GGT and ALAT values at 6 months) were analysed with models similar to those used for the co-primary variables. The CGI-S baseline score was included as a covariate in the model for CGI-I.

In the previous 6-month studies with nalmefene taken as needed, a substantial proportion of patients already reduced their drinking to < 6 heavy drinking days/month, or below medium drinking risk level in the period between screening and randomisation, i.e. prior to taking any study medication (van den Brink et al., 2013). These patients are expected not to benefit from treatment, whereas those whom continued their high alcohol consumption after initial assessment and are still drinking at high/very high risk levels at the start of treatment are expected to derive the highest clinical benefit from nalmefene. Therefore, post-hoc analyses of efficacy and safety were performed, to assess the effect of nalmefene versus placebo in those patients with a high/very high drinking risk level, at both screening and randomisation (*target population*). These analyses were performed in the same way as the pre-defined primary analyses (except that country instead of site was included as a fixed effect in the model). In order to perform these analyses, two additional datasets were thus defined:

1. The *target safety population*, comprising the *target population*, but excluding from the dataset those with no recorded study medication intake and all study medication returned; and
2. The *target efficacy population*, comprising all patients in the *target safety population* with one or more valid post-baseline assessment/s of the co-primary outcome measure.

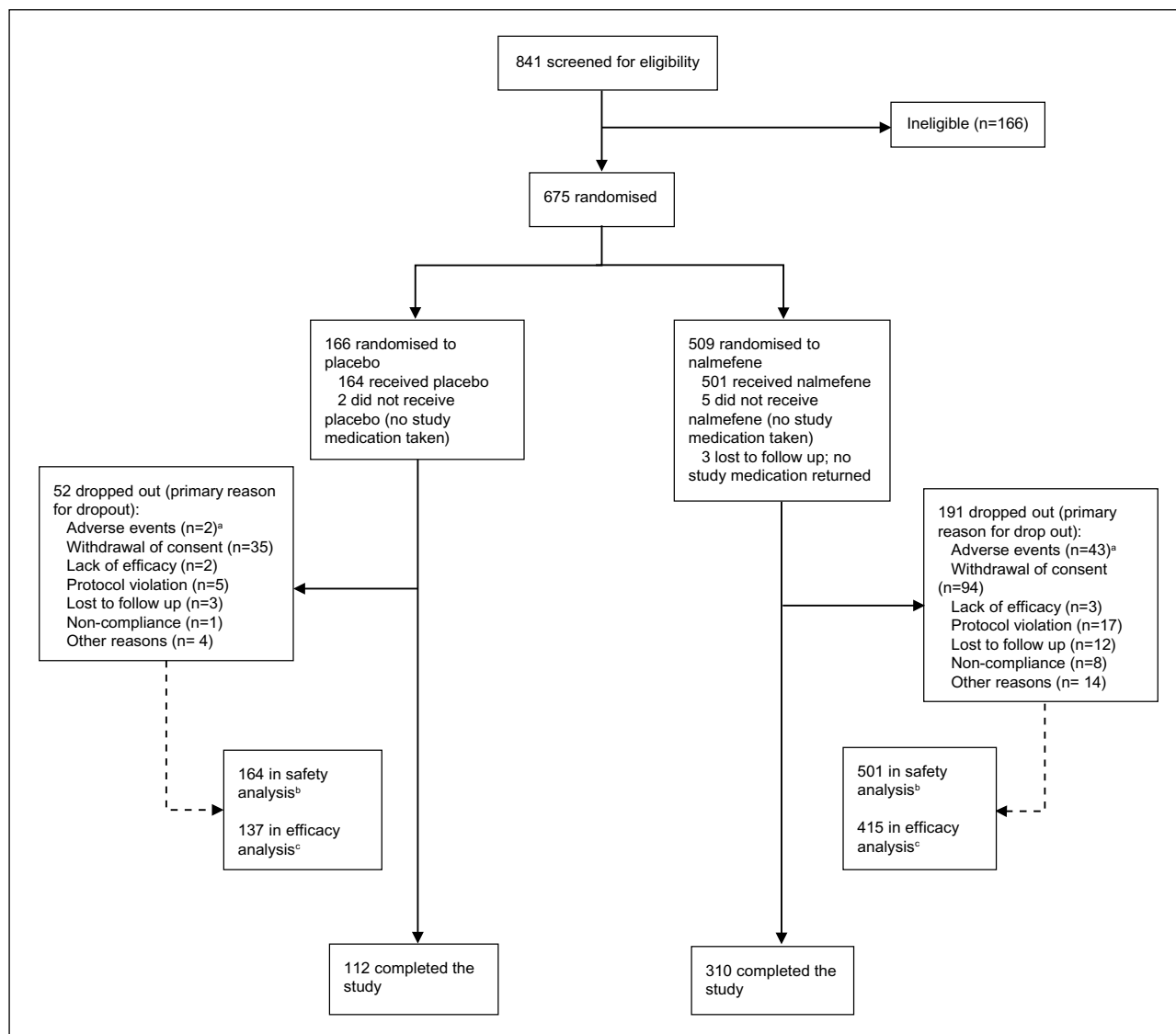


Figure 1. Trial profile.

^aAdverse events were not set to primary reason for dropout by default.

^bAll-patients-treated set, comprising all randomised patients but excluding from the dataset those with no recorded study medication intake and all study medication returned.

^cFull-analysis set, comprising all patients in the all-patients-treated set with at least one valid post-baseline assessment of alcohol consumption and an average alcohol consumption at medium risk or above according to WHO criteria (>40g/day for men, >20g/day for women) at baseline. We did not include 27 and 86 patients in the placebo and nalmefene groups, respectively, in the full-analysis set.

WHO: World Health Organisation.

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

Results

Study sample

From March 2009 to September 2009, we screened 841 patients, of whom 675 were randomised (Figure 1).

There were no clinically relevant differences in baseline demographic nor clinical characteristics between the two randomised groups (Table 1). All but four of the patients were

Caucasian, approximately 75% were men, and their mean age was 44 years. The mean age of onset of alcohol problems was 33 years.

In the month before screening, patients had on average 14 heavy drinking days and drank on average 68 grams of alcohol per day; 84% of the patients met criteria for at least medium drinking risk level. The mean CGI-S score of 3.9, the Drinker Inventory of Consequences score of 48, and the Alcohol Dependence Scale score of around 16 confirmed that these were on average moderately ill patients with significant adverse consequences of drinking. Mean values of laboratory parameters were close to (GGT: 41 IU/L; ALAT: 28 IU/L; MCV: 96 fL) or slightly

Table 1. Demographics and baseline clinical characteristics. Data are represented as mean (SD) or number of participants (%).

All-patients-randomised set		Placebo	Nalmefene
		166	509
Race	Caucasian	165 (99.4%)	506 (99.4%)
Sex	Men	127 (76.5%)	393 (77.2%)
Age (years)		44.3 (12.0)	44.3 (11.2)
BMI (kg/m ²)		25.8 (4.3)	26.0 (4.2)
Age at the onset of drinking problems		33.4 (11.3)	33.4 (11.6)
Drinking risk level ^a	Unknown		1 (0.2%)
	Low	26 (15.7%)	79 (15.5%)
	Medium	49 (29.5%)	167 (32.8%)
	High	59 (35.5%)	148 (29.1%)
	Very high	32 (19.3%)	114 (22.4%)
Total monthly heavy drinking days (days) ^a		13.7 (6.0)	14.1 (6.2)
Total alcohol consumption (g alcohol/day) ^a		68.0 (40.6)	68.6 (40.0)
Clinical Global Impression - Severity of Illness		3.88 (1.03)	3.95 (1.12)
γ -glutamyltransferase (IU/L) ^b		41.0	40.9
Alanine aminotransferase (IU/L) ^b		26.5	28.5
Mean corpuscular volume (fL) ^b		95.8	96.4
Carbohydrate-deficient transferrin (%)		2.51 (1.47)	2.55 (1.53)
Drinker inventory of consequences total score		48.9 (25.0)	48.1 (23.5)
Alcohol dependence scale total score		16.4 (7.6)	16.1 (6.6)
Brief Measure of Readiness to Change Questionnaire 'readiness to change' subscale score		7.4 (2.1)	7.5 (2.0)
Any current psychiatric comorbidity ^c	Yes	9 (5.4%)	19 (3.7%)
Current major depressive episode ^c	Yes	3 (1.8%)	5 (1.0%)
Current social phobia/anxiety disorder ^c	Yes	1 (0.6%)	2 (0.4%)
Current drug dependence (non-alcohol) ^c	Yes	2 (1.2%)	0 (0.0%)
Current psychotic syndrome ^c	Yes	1 (0.6%)	1 (0.2%)
Living with someone	Yes	140 (84.3%)	436 (85.6%)
Active employment	Yes	107 (64.5%)	333 (65.4%)
Higher education	Yes	51 (30.7%)	165 (32.4%)
Previously treated for alcohol dependence	Yes	61 (36.7%)	171 (33.6%)
Previously treated for alcohol withdrawal symptoms	Yes	48 (28.9%)	137 (26.9%)
Family history of alcohol problems	Yes	69 (41.6%)	263 (51.7%)
< 6 Heavy drinking days or drinking risk level < medium at randomisation ^d	Yes	58 (42.3%)	157 (37.8%)

^aBased on Timeline Follow-back data from the month preceding the screening visit.

^bGeometric mean.

^cAssessed with Mini-International Neuropsychiatric Interview.

^dPatients 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*.

BMI: Body mass index; IU: international units.

above the reference ranges (CDT: 2.53%). The majority of patients had not previously been treated for alcohol dependence (66%) nor alcohol withdrawal (73%).

The *all-patients-treated set* comprised 665 patients and the *full-analysis set* comprised 552 patients. Importantly, 215 of these 552 patients (39%) 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).

Patients with high/very high risk levels at screening, who continued their high alcohol consumption at the start of treatment, constituted the *target population*. Baseline characteristics for the

target population were similar to the total population; except for a higher total alcohol consumption, a larger number of heavy drinking days, higher mean GGT levels (GGT: 54 IU/L; ALAT: 30 IU/L), higher mean CDT levels (CDT: 2.95%), and an even lower proportion of patients with previous treatment for alcohol dependence (Supplementary material: Table S1). There were no clinically relevant differences in baseline demographic nor clinical characteristics between the *target groups* receiving nalmefene or placebo (Table S1).

During the study, 52 (32%) of the placebo-treated patients and 191 (38%) of the nalmefene-treated patients dropped out; the most frequent primary reason for dropping out was withdrawal of

Table 2. Distribution of percentage of days with study medication intake.

Treatment group	Patients	Summary Statistics	Timeline Follow-back days	Study medication days	% Days with study medication ^a
Placebo	163	Mean	297	152	52.8
		10th percentile	61	24	14.0
		90th percentile	374	344	96.4
Nalmefene	499	Mean	276	135	48.4
		10th percentile	29	7	8.7
		90th percentile	372	335	94.1

^aDistribution of the individual patient percentages of days with study medication intake.

Only patients in the *all-patients-treated set* with Timeline Follow-back study medication records are included.

consent, in both the placebo group and the nalmefene group (Figure 1). A total of 112 patients (68%) in the placebo group and 310 (62%) in the nalmefene group completed the study.

On average, both patients receiving placebo and nalmefene took their study medication on approximately one-half of the days in the study (Table 2).

Efficacy

Total population. At month 6, the co-primary outcome variables showed no statistically significant differences between the treatment groups: The group difference in the change in heavy drinking days was -0.9 days/month (95% CI $-2.1; 0.4$; $p = 0.160$) and the group difference in the change of total alcohol consumption was -3.5 g/day (95% CI $-9.2; 2.2$; $p = 0.232$) (Figure 2; Table 3).

However, at month 13 nalmefene was more effective than placebo both in the reduction of heavy drinking days (group difference: -1.6 days/month [95% CI $-2.9; -0.3$]; $p = 0.017$) and total alcohol consumption (group difference: -6.5 g/day last month [95% CI $-12.5; -0.4$]; $p = 0.036$) (Figure 2; Table 3).

With the exception of the baseline observation carried forward imputation for total alcohol consumption, the sensitivity analyses using different procedures to handle missing data showed very similar results, but with smaller group differences (Supplementary material: Table S2).

The key secondary outcome measure, drinking risk level response at month 6, showed no differences between the treatment groups (76% responders for placebo and 78% responders for nalmefene, corresponding to an OR of 1.06 [95% CI 0.64; 1.74]; $p = 0.816$).

A decrease in the CGI-S score from baseline was observed in both treatment groups (Figure 3), with an effect of nalmefene, compared to the placebo group, at month 6 (group difference: -0.18 [95% CI $-0.37; -0.00$]; $p = 0.046$) but not at month 13 (group difference: -0.22 [95% CI $-0.44; 0.01$]; $p = 0.056$).

We observed a decrease in the CGI-I score from baseline, in both the treatment groups (Figure 3), with a favourable effect of nalmefene compared to the placebo seen only at month 13: group difference month 6: -0.14 (95% CI $-0.36; 0.08$; $p = 0.217$); and a group difference at month 13: -0.26 (95% CI $-0.50; -0.03$; $p = 0.029$).

For GGT and ALAT, the analysis showed similar improvements from baseline to month 6 in both treatment groups

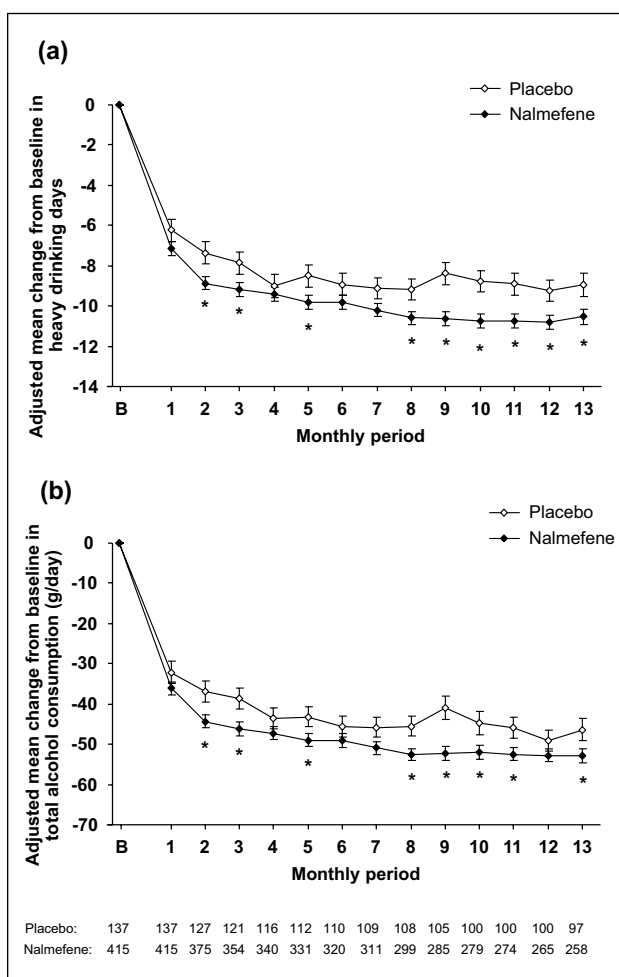


Figure 2. Change in alcohol consumption in the *full-analysis set*. (a) Adjusted mean change from baseline in monthly heavy drinking days. (b) Adjusted mean change from baseline in monthly total alcohol consumption (g/day). Baseline data for heavy drinking days and total alcohol consumption were derived 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. Bars indicate SEs. * $p < 0.05$ (difference to placebo). B: Baseline; SE: standard error.

Table 3. Baseline values and co-primary outcome variables at months 6 and 13, in the *full-analysis set*. Baseline values were based on observed cases; changes from baseline and differences to placebo were based on mixed model repeated measures values.

Efficacy variable	N	Placebo	N	Nalmefene	Difference to placebo	
					Mean	p-value
Number of heavy drinking days						
Baseline \pm SD	137	14.7 \pm 6.1	415	15.2 \pm 6.1		
Adjusted change from baseline to mo 6 \pm SE	110	- 8.9 \pm 0.6	320	- 9.8 \pm 0.4	- 0.9 [- 2.1; 0.4]	0.160
Adjusted change from baseline to mo 13 \pm SE	97	- 9.0 \pm 0.6	258	- 10.5 \pm 0.4	- 1.6 [- 2.9; - 0.3]	0.017
Total alcohol consumption (g/day)						
Baseline \pm SD	137	75 \pm 41	415	75 \pm 39		
Adjusted change from baseline to mo 6 \pm SE	110	- 45.6 \pm 2.6	320	- 49.1 \pm 1.6	- 3.5 [- 9.2; 2.2]	0.232
Adjusted change from baseline to mo 13 \pm SE	97	- 46.3 \pm 2.7	258	- 52.8 \pm 1.8	- 6.5 [- 12.5; - 0.4]	0.036

g: grams ; mo: month; SD: standard deviation; SE: standard error.

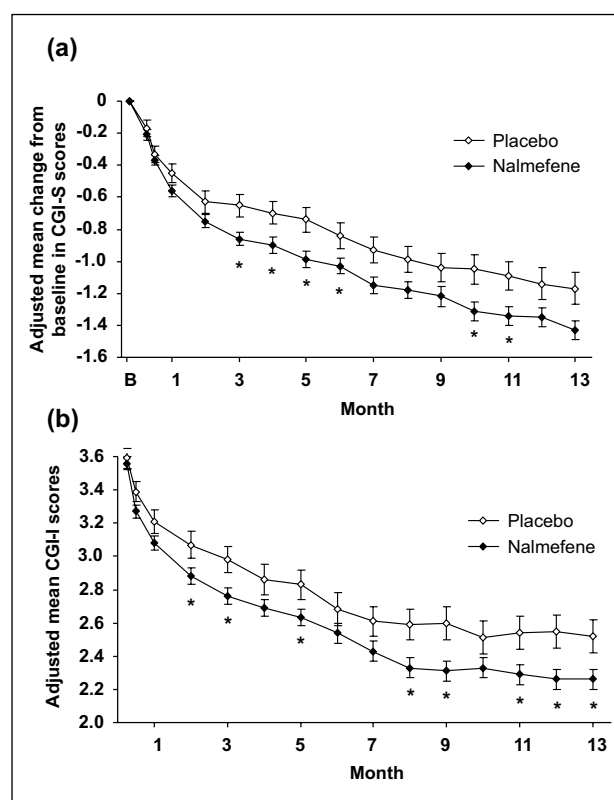
(Table 4); but at month 13 there was a favourable effect of nalmefene, compared to the placebo (GGT: ratio 0.78 [95% CI 0.67; 0.90]; $p = 0.001$; ALAT: ratio 0.88 [95% CI 0.79; 0.99]; $p = 0.037$). For CDT, the analysis showed a favourable effect of nalmefene, compared to placebo, at month 6 (- 0.27 [95% CI - 0.51; - 0.04]; $p = 0.022$) but not at month 13 (- 0.25 [95% CI - 0.56; 0.05]; $p = 0.105$) (Supplementary material, Table S3).

Post-hoc analysis of the target efficacy population. A post-hoc efficacy analysis was performed in the 183 patients (33% of the *full-analysis set*) with a high/very high drinking risk level, at both screening and randomisation, and at least one post-baseline efficacy assessment (*target efficacy population*).

At month 6, nalmefene treatment in this *target population* did not result in a statistically significant larger reduction of the mean number of heavy drinking days, compared to placebo treatment (group difference: - 2.6 days/month [95% CI - 5.5; 0.2]; $p = 0.071$); but nalmefene was more effective than placebo in reducing the mean total alcohol consumption (- 15.3 g/day last month [95% CI - 29.1; - 1.5]; $p = 0.031$) (Figure 4, Table 5).

Data at month 13 showed an effect of nalmefene compared to placebo, both for the number of heavy drinking days (group difference: - 3.6 days/month [95% CI - 6.5; - 0.7]; $p = 0.016$) and total alcohol consumption (group difference: - 17.3 g/day last month [95% CI - 30.9; - 3.8]; $p = 0.013$) (Figure 4 and Table 5).

The decrease in the CGI-S score was similar in both treatment groups, at both month 6 and month 13 (Supplementary material, Figure S1). We observed a decrease in the CGI-I score from the baseline, in both treatment groups (Supplementary Figure S1), with no significant differences between the treatment groups at month 6 nor month 13: Group difference at month 6: - 0.35 (95% CI - 0.77; 0.07; $p = 0.104$); group difference at month 13: - 0.34 (95% CI - 0.77; 0.08; $p = 0.113$) (Supplementary Figure S1). The liver parameters GGT and ALAT improved from baseline to month 6 in both the treatment groups, with a difference in favour ($p < 0.05$) of nalmefene for GGT also observed at month 13 (Supplementary Table S4). For CDT, our analysis showed no significant differences between the treatment groups at either month 6 or 13 (Supplementary Table S3).

**Figure 3.** Change in Clinical Global Impression in the *full-analysis set*. Bars indicate SEs. (a) Adjusted change from baseline in CGI-S scores. (b) Adjusted CGI-I scores.

* $p < 0.05$ (difference to placebo).

B: baseline; CGI-I: Clinical Global Impression - Improvement; CGI-S: Clinical Global Impression - Severity of Illness; SE: standard error.

Safety and tolerability

During the study, 103 (63%) of the patients in the placebo group and 377 (75%) of the patients in the nalmefene group had treatment-emergent adverse events (Table 6). Of the most common treatment-emergent adverse events (incidence $\geq 5\%$), we found that nausea, insomnia, dizziness, vomiting, fatigue and decreased

Table 4. Secondary efficacy variables: GGT and ALAT at months 6 and 13, in the *full-analysis set*.

Efficacy variable	Placebo		Nalmefene		Ratio to placebo		
	N	Geometric mean	N	Geometric mean	Ratio	95% CI	p-value
γ -glutamyl transferase (IU/L)							
Baseline	137	45.4	414	41.6			
Adjusted geometric mean at month 6	108	34.5	319	32.2	0.93	[0.83; 1.05]	0.273
Adjusted geometric mean at month 13	98	41.2	259	32.0	0.78	[0.67; 0.90]	0.001
Alanine aminotransferase (IU/L)							
Baseline	137	26.9	415	28.6			
Adjusted geometric mean at month 6	108	25.8	318	25.6	0.99	[0.90; 1.10]	0.916
Adjusted geometric mean at month 13	97	27.8	259	24.6	0.88	[0.79; 0.99]	0.037

CI: Confidence interval; IU: international units.

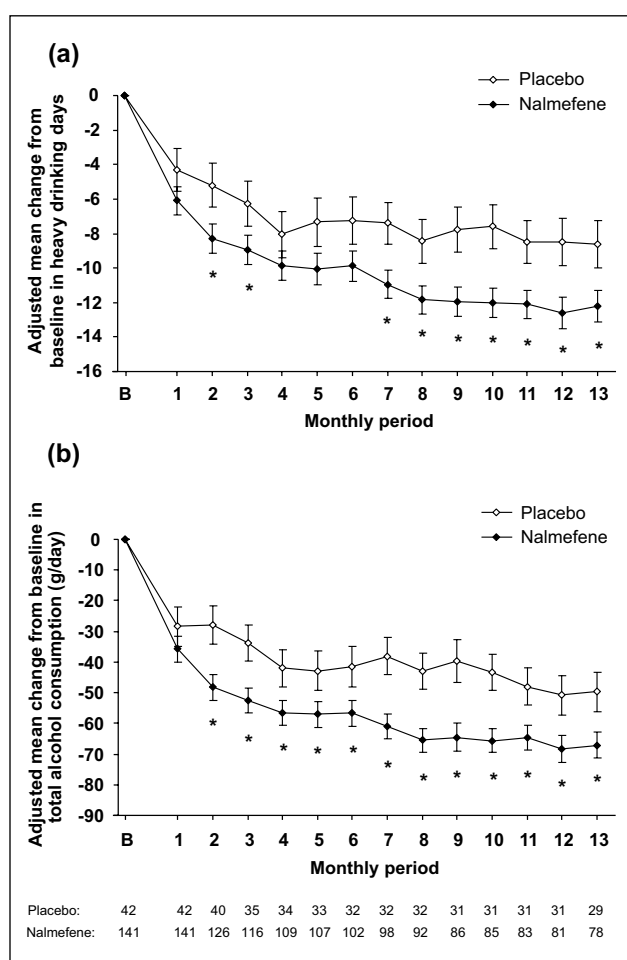


Figure 4. Change in alcohol consumption in the *target efficacy population*. (a) Adjusted mean change from baseline, in monthly heavy drinking days. (b) Adjusted mean change from baseline, in monthly total alcohol consumption (g/day). Baseline data for heavy drinking days and total alcohol consumption 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). Bars indicate SEs.

B: Baseline; SE: standard error.

appetite had an incidence two times higher in the nalmefene group than in the placebo group. The majority of the most common adverse events were transient (1–7 days) and the vast majority (97%) were mild or moderate in intensity. A total of 55% of the patients with the most common adverse events in the nalmefene group experienced these events within 1 day after the first dose of the study medication; the vast majority (95%) of these adverse events were mild or moderate in intensity. A total of 62 patients dropped out, due to treatment-emergent adverse events: 5 patients (3.0%) in the placebo group and 57 (11.4%) in the nalmefene group (Table 6). Treatment-emergent adverse events with an incidence $\geq 1.0\%$ that led to dropout comprised dizziness, nausea, disturbances in attention and insomnia, in the nalmefene group.

Serious adverse events were reported for 44 patients (including 1 patient in the placebo group, with a pre-treatment serious adverse event): 9 patients in the placebo group (5.4%) and 35 patients in the nalmefene group (6.9%). No serious adverse event was reported in more than one patient in either treatment group, except for alcohol withdrawal syndrome (8 patients in the nalmefene group), atrial fibrillation (2 patients in the nalmefene group), fall (2 patients in the nalmefene group) and disorientation (2 patients in the nalmefene group). The majority of serious adverse events in the placebo group (88%) and the nalmefene group (76%) were considered by the investigator to be not related to the study medication. 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, with the exception of alcohol withdrawal syndrome.

The adverse event profile for the *target safety population* was similar to that of the total population (Table 6).

One patient died during the study: A 44-year-old man in the nalmefene group suffered a traumatic brain injury, as a passenger in a car accident. This event was considered by the investigator to be not related to the study medication.

Eight patients were identified as having potentially suicide-related adverse events (three were on placebo (2%) and five on nalmefene (1%)): Three patients in each treatment group had an intentional overdose (overdose of study medication: >1 tablet in 1 day). All events were non-serious and mild (none of the patients took more than 2 doses of study medication on any one occasion), except for one patient in the nalmefene group, who took 14 doses of the study medication, for which the event was severe.

Table 5. Baseline values and co-primary outcome variables at months 6 and 13 month month in the *target efficacy population*. Baseline values were based on observed cases; changes from baseline and differences to placebo were based on mixed model repeated measures values.

Efficacy variable	N	Placebo	N	Nalmefene	Difference to placebo	
					Mean	p-value
Number of heavy drinking days						
Baseline \pm SD	42	18.6 \pm 6.4	141	19.1 \pm 6.3		
Adjusted change from baseline to mo 6 \pm SE	32	- 7.2 \pm 1.4	102	- 9.9 \pm 0.9	- 2.6 [- 5.5; 0.2]	0.071
Adjusted change from baseline to mo 13 \pm SE	29	- 8.6 \pm 1.4	78	- 12.2 \pm 0.9	- 3.6 [- 6.5; - 0.7]	0.016
Total alcohol consumption (g/day)						
Baseline \pm SD	42	100.6 \pm 46.9	141	100.4 \pm 45.0		
Adjusted change from baseline to mo 6 \pm SE	32	- 41.4 \pm 6.6	102	- 56.7 \pm 4.3	- 15.3 [- 29.1; -1.5]	0.031
Adjusted change from baseline to mo 13 \pm SE	29	- 49.8 \pm 6.4	78	- 67.1 \pm 4.3	- 17.3 [- 30.9; -3.8]	0.013

g: Grams; mo: month; SD: standard deviation; SE: standard error.

Table 6. Adverse events. Data given as the number of patients (%).

	<i>All-patients-treated set</i>		<i>Target safety population</i>	
	Placebo (n = 164)	Nalmefene (n = 501)	Placebo (n = 42)	Nalmefene (n = 144)
Patients with treatment-emergent adverse events	103 (62.8)	377 (75.2)	26 (61.9)	112 (77.8)
Treatment-emergent adverse events (\geq 5% in the <i>all-patients-treated set</i>)				
Nausea	9 (5.5)	112 (22.4)	1 (2.4)	37 (25.7)
Insomnia	11 (6.7)	74 (14.8)	1 (2.4)	20 (13.9)
Dizziness	6 (3.7)	73 (14.6)	1 (2.4)	26 (18.1)
Headache	13 (7.9)	62 (12.4)	2 (4.8)	14 (9.7)
Vomiting	2 (1.2)	57 (11.4)	1 (2.4)	15 (10.4)
Nasopharyngitis	19 (11.6)	54 (10.8)	3 (7.1)	12 (8.3)
Somnolence	8 (4.9)	42 (8.4)	3 (7.1)	10 (6.9)
Fatigue	3 (1.8)	27 (5.4)	2 (4.8)	9 (6.3)
Decreased appetite	2 (1.2)	26 (5.2)	0 (0.0)	8 (5.6)
Accidental overdose ^a	9 (5.5)	9 (1.8)	4 (9.5)	5 (3.5)
Fall	11 (6.7)	7 (1.4)	4 (9.5)	3 (2.1)
Patients with treatment-emergent adverse events leading to dropout	5 (3.0)	57 (11.4)	0 (0.0)	20 (13.9)
Treatment-emergent adverse events leading to dropout (\geq 1.0% in the <i>all-patients-treated set</i>)				
Dizziness	0 (0.0)	12 (2.4)	0 (0.0)	7 (4.9)
Nausea	0 (0.0)	10 (2.0)	0 (0.0)	2 (1.4)
Disturbances in attention	0 (0.0)	5 (1.0)	0 (0.0)	1 (0.7)
Insomnia	0 (0.0)	5 (1.0)	0 (0.0)	3 (2.1)
Patients with serious adverse events ^b	9 (5.4)	35 (6.9) ^c	1 (2.4)	12 (8.3)

^aDefined as > 1 tablet of study medication in 1 day.

^bPercentages were based on the *all-patients-randomised set*.

^cIncluded one patient who died of traumatic brain injury.

One patient in the nalmefene group reported intentional self-injury, and another patient in the nalmefene group had a serious adverse event of suicidal behaviour.

A total of 18 patients (2 (1%) on placebo and 16 (3%) on nalmefene) had one or more of selected psychiatric adverse events. Two of these events were serious (disorientation in two patients in the nalmefene group: one severe and one moderate); the rest of the events were non-serious, and with the exception of

one severe event of disorientation, mild or moderate. The onset of the events appeared to be associated with treatment initiation; the duration was short, typically lasting 1–3 days. All patients recovered from the events.

There were no apparent trends in the incidence of clinically-relevant laboratory values between the two treatment groups, with the exception of high ALAT and ASAT values (both were higher in the nalmefene, compared to the placebo group) and

GGT values (higher in the placebo, compared to the nalmefene group). No clinically relevant changes over time nor differences between treatment groups were seen in vital signs, weight, electrocardiogram parameters nor total POMS scores.

Discussion

This study is the third study in the completed clinical Phase III program using nalmefene as-needed to reduce alcohol consumption in patients with a DSM-IV diagnosis of alcohol dependence. Patients were predominantly middle-aged men, with more than 50% having a high or very high drinking risk level at baseline and an average baseline consumption of almost 70 g/d alcohol, which is somewhat lower than in the two previous studies (Gual et al., 2013; Mann et al., 2013), reflecting the fact that patients with a low drinking risk level at screening were also included in the study. In line with European Medicines Agency (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. In contrast to the two previously mentioned studies, patients with a stable comorbid psychiatric disorder were eligible for inclusion. This study population is comparable to patients that are likely to present in primary care (Willenbring et al., 2009). Similar to the nalmefene as-needed studies by Mann et al. (2013) and Gual et al. (2013), the majority of the patients had never received any treatment, despite their alcohol problems having started more than 10 years before. The nalmefene treatment obviously has the potential to engage alcohol-dependent patients in treatment, whom may otherwise not have sought help.

Compared to baseline, there was a substantial reduction in alcohol consumption in both treatment conditions, on both coprimary outcome measures. Nalmefene was better, although not significantly so, compared to placebo, in reducing the number of heavy drinking days and total alcohol consumption at the 6-month time point in this population of alcohol-dependent patients with relatively low alcohol consumption levels, despite the patients with low drinking risk levels being excluded from the pre-specified efficacy analysis. Almost 40% of the patients in the *full-analysis set* substantially decreased their alcohol consumption already in the period between screening and randomisation, i.e. prior to taking any study medication. Inclusion of this large proportion of 'early reducers' in the pre-specified efficacy analysis may have resulted in a substantial underestimation of the treatment effect.

When analysing the *target efficacy population*, i.e. the patients whom continued their high/very high level of alcohol consumption after their initial assessment for the study and were still drinking at high/very high drinking risk levels at the beginning of treatment, there was a significant effect of nalmefene on the reduction of total alcohol consumption (group difference: -15.3 g/day [95% CI -29.1 ; -1.5]; $p = 0.031$) and a borderline significant effect on the reduction of the number of heavy drinking days (group difference: -2.6 days [95% CI -5.5 ; 0.2]; $p = 0.071$) at 6 months. These effect sizes are similar to those of the recently published, pooled subgroup analysis of patients with high/very high drinking risk levels from the two previous nalmefene as-needed studies (van den Brink et al., 2013). These findings further support that nalmefene as-needed is especially effective in patients with high/very high drinking risk levels at the start of treatment.

There was a high retention rate: a total of 62% of the nalmefene-treated patients in the total population completed the 1-year study. This figure is larger than reported in the two previous studies with nalmefene, of a much shorter duration (Gual et al., 2013; Mann et al., 2013). The high retention rate indicates that, for the majority of the patients, nalmefene was well accepted over an extended period. Furthermore, the effect of nalmefene as-needed on the number of heavy drinking days and total alcohol consumption was maintained over the full study period, as is evident from the fact that the differences between nalmefene and placebo were in favour of nalmefene at most time points, including the month 13 assessment. Nalmefene provided a rapid and sustained effect, reducing total alcohol consumption already within the first month and by 67% after 1 year of treatment. Importantly, these long-term effects of nalmefene on the reduction of self-reported alcohol consumption were supported by the data from the long-term effects on CGI-I and liver parameters (GGT and ALAT).

The tolerability and safety profile was as expected from previously published data (Anton et al., 2004; Gual et al., 2013; Karhuvaara et al., 2007; Mann et al., 2013; Mason et al., 1994, 1999; van den Brink et al., 2013) and reflects the pharmacological profile of nalmefene. There were similar proportions of patients in the placebo and nalmefene group having serious adverse events (5.4% versus 6.9%) and a larger proportion of patients with treatment-emergent adverse events leading to dropout, in the nalmefene group compared to the placebo group (3.0% versus 11.4%). The adverse event profile for the *target safety population* was similar to that of the total population. Overall, long-term use of nalmefene as-needed was well tolerated (also evident from the high retention rate) and no safety issues were raised in this study.

The main limitation of this study is the large, non-specific treatment response with almost 40% substantially reducing their drinking prior to the start of treatment. At randomisation, these patients consumed such a small amount of alcohol that there was little room for further improvement, irrespective of treatment. Motivational factors, expectancy and natural course could explain why these patients self-initiated a reduction in alcohol consumption immediately after they were informed about the study and consented to participate, and before they had started on any formal treatment. These patients may represent excessive drinkers whom 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.) This is a phenomenon that has been observed in other alcohol treatment studies, including recently published studies by Mann et al. (2013) and Gual et al. (2013), and can indeed have an impact on study outcome (Epstein et al., 2005; Gual et al. 2013; Litten et al., 2012).

The results from this study should also be interpreted in view of the fact that the study population was limited by the selection criteria, although alcohol-dependent patients with stable comorbid psychiatric disorders were allowed in the study. The levels of psychiatric comorbidity were lower, compared to the levels described in general population studies (Kessler et al. 1996), most likely as a result of the selection criteria limiting the degree of comorbidity. Many treatment-seeking, alcohol-dependent patients have unstable comorbid psychiatric disorders that require additional or integrated treatments, and some may even require total abstinence from all psychoactive drugs, including alcohol (van Amsterdam and van den Brink, 2013). Additional studies

are needed to show the full value of nalmefene in these complex patients.

In conclusion, nalmefene was well-tolerated in the long-term treatment of patients with alcohol dependence. Although failing to achieve significance on the co-primary endpoints for the total population, the current study showed that nalmefene was an effective treatment for alcohol-dependent patients whom continued to have high/very high risk drinking levels 1–2 weeks after an assessment of their alcohol use, similar to a brief intervention. Targeting the population who did not reduce their alcohol consumption after an initial period of observation is highly clinically relevant, given that a 2-step approach for patients unable to change their behaviour after initial counselling is typically used in routine clinical practice across many different disease areas. Treatment retention was high. The treatment effect lasted for at least 1 year, with clinically-relevant effects in terms of self-reported reductions of alcohol use and laboratory measures of improved liver function later in the treatment.

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Conflict of interest

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 given paid expert testimony for Schering-Plough. Per Sørensen and Lars Torup are Lundbeck employees. Karl Mann has received research grants from Schering-Plough, Alkermes, Lundbeck, McNeil and Merck; was a paid consultant to Alkermes and Desitin, and is a consultant to Lundbeck and Pfizer; and has received speaker fees from Lundbeck. Antoni Gual has received honoraria and travel grants from Lundbeck, Janssen and Servier.

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