ESENSE 1 - RANDOMISED CONTROLLED 6-MONTH STUDY OF AS-NEEDED NALMEFENE: SUBGROUP ANALYSIS OF ALCOHOL DEPENDENT PATIENTS WITH HIGH DRINKING RISK LEVEL

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Introduction

- Nalmefene: dual-acting opioid system modulator with distinct μ, δ, and κ-receptor profile; proposed mechanism of action: to restore the balance of a dysregulated motivational system by reducing the reinforcing effect of alcohol, and thereby reducing the urge to drink alcohol
- Nalmefene as-needed significantly reduce total alcohol consumption and number of heavy drinking days and significantly improve liver function and clinical status (Mann *et al.* 2012)
- Large non-specific treatment response: 18% of the patients substantially reduced drinking between screening and randomisation
- The benefit of nalmefene is here further studied in the subgroup of patients who after initial assessment still were drinking at high drinking risk levels at the start of treatment

Objectives

- To evaluate the efficacy and safety of as-needed use of nalmefene 18mg *versus* placebo in reducing the monthly number of heavy drinking days (HDDs; ≥60g/day for men, ≥40g/day for women) and the monthly total alcohol consumption (TAC; g/day) at month 6 in the subgroup of alcohol-dependent patients with high drinking risk level at both screening and randomisation from the randomised controlled trial ESENSE 1 (NCT00811720)

Methods

Study population: Subgroup of men and women ≥18 years with a primary diagnosis of DSM-IV alcohol dependence and alcohol consumption ≥WHO high drinking risk level (>60 g/day for men and >40 g/day for women) at both screening and randomisation. Patients received placebo or nalmefene (1:1).

Intervention: As-needed dosing principle: one tablet on each day that patient perceived risk of drinking alcohol. All patients took part in motivational and adherence-enhancing intervention (BRENDA) to support behavioural change and enhance adherence to treatment.

Assessments: Monthly (1 month = 28 consecutive days) drinking variables derived from the Timeline Follow-back (TLFB).

Outcome measures and statistical analysis:

- Safety analyses based on the *patients treated set*
- Efficacy analyses based on the *analysis set* = all patients in *patients treated set* with ≥1 valid post-baseline assessment of co-primary outcome measures
- Co-primary outcome measures: changes from baseline at month 6 in the number of HDDs and TAC (mixed model repeated measures [MMRM])
- Secondary outcome measures: Proportions of responders (two-category downshift in drinking risk level) (logistic regression; MMRM-predicted TAC-values), changes from baseline in CGI-S, CGI-I, log-transformed γ-glutamyltransferase (GGT), and alanine aminotransferase (ALAT)(MMRM)

Results

Patient baseline characteristics

Figure 1. Trial profile.

	Placebo	Nalmefene
Patients with high drinking risk level at both screening and randomisation	170	180
Not treated	1	1
Patients treated set	169	179
Patients dropping out:		
Adverse events*	13	45
Lack of efficacy	17	13
Non-compliance	0	9
Protocol violation	4	9
Withdrawal of consent	19	18
Lost to follow-up	6	6
Other	3	2
Patients completed	107	97
Analysis set	167	171

*Adverse events were not by default set to primary reason for dropout.

- No differences in baseline demographic or clinical characteristics between the groups (Table 1)

Table 1. Demographics and baseline clinical characteristics

Patients randomised		Placebo (170)	Nalmefene (180)
Race	Caucasian	170 (100%)	180 (100%)
Sex	Men	105 (61.8%)	114 (63.3%)
Age (years)		52.9 (8.8)	50.9 (10.0)
Body Mass Index, kg/m²		26.9 (4.2)	26.7(4.6)
Age at onset of drinking problem		38.4 (12.1)	37.9 (13.3)
Total monthly heavy drinking days (days)		23.1 (5.5)	23.0 (5.9)
Total alcohol consumption (g alcohol/day)		98.6 (40.5)	102 (42.9)
Clinical global impression – severity of illness		4.2 (1.4)	4.1 (1.4)
γ-glutamyltransferase(IU/L)*		60.1	56.2
Alanine aminotransferase (IU/L)*		29.4	29.6
Mean corpuscular volume (fL)*		96.6	97.3
Carbohydrate-deficient transferrin(%)		2.6 (1.3)	2.7 (1.6)
Drinker inventory of consequences total score		35.3 (17.7)	35.0 (18.1)
Alcohol dependence scale total score		11.8 (4.8)	12.7 (5.6)
Living alone	Yes	60 (35.3%)	55 (30.6%)
Unemployed	Yes	31 (18.2%)	40 (22.2%)
Previously treated for alcohol dependence	Yes	45 (26.5%)	46 (25.6%)
Previously treated for alcohol withdrawal symptoms	Yes	31 (18.2%)	31 (17.2%)
Family history of alcohol problem	Yes	117 (68.8%)	112 (62.2%)

*Geometric mean; Data are mean (SD) or number of participants (%); SD=standard deviation.

Efficacy

- Observed primary efficacy data are presented in Table 2

Table 2. Baseline and month 6 efficacy variables (OC)

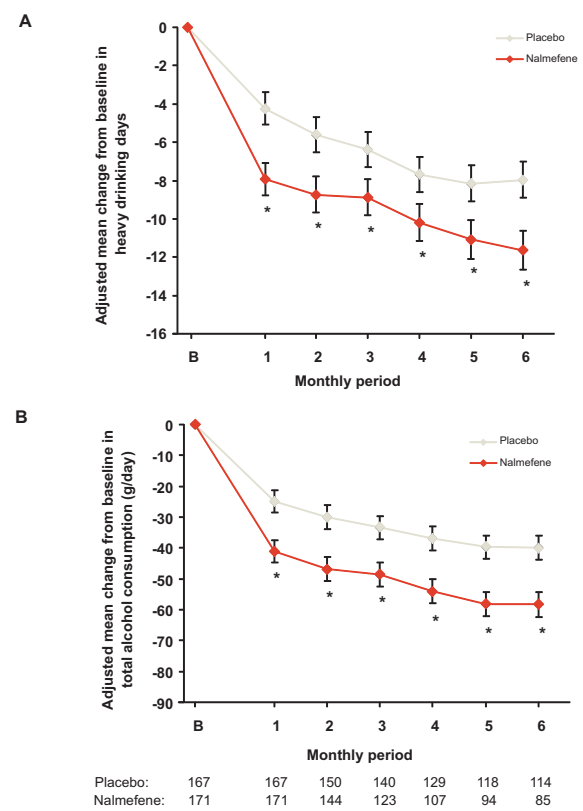
Efficacy Variable	Placebo N	Placebo Mean ± SD	Nalmefene N	Nalmefene Mean ± SD
Monthly number of heavy drinking days				
Baseline	167	23.1 ± 5.4	171	23.0 ± 5.9
Month 6	114	14.0 ± 9.4	85	9.3 ± 8.3
Monthly total alcohol consumption (g/day)				
Baseline	167	98.7 ± 40.5	171	102 ± 42.9
Month 6	114	57.0 ± 41.4	85	39.6 ± 30.0

SD=standard deviation. OC=observed cases.

Co-primary outcome measures (MMRM)

- Statistically significant reduction in the number of HDDs and TAC in favour of nalmefene already at month 1 (Figure 2)
- Mean number of HDDs decreased from 23.0 to 11.4 days/month and the mean TAC decreased from 102 to 43.9 g/day in the nalmefene group at month 6
- At month 6: Statistically significant effect of nalmefene compared to placebo in reducing the number of HDDs (-3.7 days/month [95% CI -5.9; -1.5]; p=0.0010), and the TAC (-18.3 g/day [95% CI -26.9; -9.7]; p<0.0001)

Figure 2. Change in alcohol consumption.

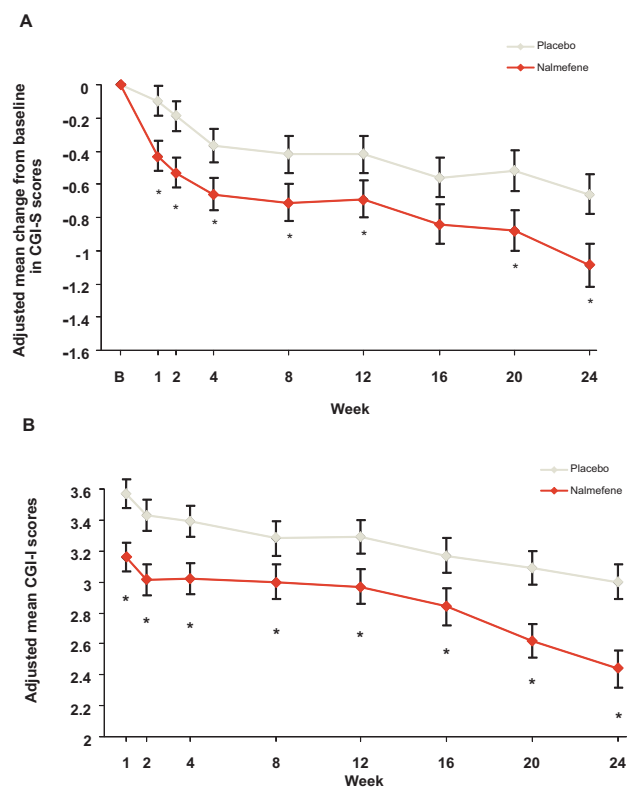


(A) Adjusted mean change from baseline in monthly heavy drinking days. (B) Adjusted mean change from baseline in monthly total alcohol consumption. Values are means ± SE; *=p<0.05 compared to placebo; B=baseline

Secondary outcome measure

- The drinking risk level-response rate at month 6 (proportion of patients with a two-category downshift in drinking risk level) was 43% for placebo and 61% for nalmefene, corresponding to an odds ratio of 2.15 [95% CI: 1.38 to 3.36]; p=0.0006
- Greater mean improvements in the CGI scores in the nalmefene group that in the placebo group (Figure 3)

Figure 3. Change in Clinical Global Impression



(A) Adjusted mean change from baseline in Clinical Global Impression-Severity of Illness (CGI-S) scores. (B) Adjusted mean Clinical Global Impression-Global Improvement (CGI-I) scores. Values are means ± SE; *=p<0.05 compared to placebo; B=baseline.

- Significant improvements in the liver enzyme GGT from baseline to week 24 in the nalmefene group compared to placebo (Table 3)

Table 3. Liver parameters: GGT and ALAT at week 24

Efficacy variable	Placebo N	Placebo Geometric mean	Nalmefene N	Nalmefene Geometric mean	Ratio to placebo Ratio	95% CI	p-value
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

CI=confidence interval.

Tolerability and safety

Table 4. Adverse events

	Placebo (n=169)	Nalmefene (n=179)
Treatment-emergent adverse events*	124 (73.4)	149 (83.2)
Treatment-emergent adverse events (≥5%)*		
Dizziness	12 (7.1)	56 (31.3)
Nausea	12 (7.1)	51 (28.5)
Fatigue	16 (9.5)	30 (16.8)
Sleep disorder	1 (0.6)	28 (15.6)
Headache	18 (10.7)	27 (15.1)
Insomnia	3 (1.8)	20 (11.2)
Nasopharyngitis	27 (16.0)	18 (10.1)
Vomiting	5 (3.0)	15 (8.4)
Decreased appetite	3 (1.8)	11 (6.1)
Hyperhidrosis	3 (1.8)	11 (6.1)
Back pain	9 (5.3)	10 (5.6)
Dry mouth	3 (1.8)	9 (5.0)
Hypoaesthesia	1 (0.6)	9 (5.0)
Diarrhoea	12 (7.1)	8 (4.5)
Accidental overdose	11 (6.5)	4 (2.2)
Treatment-emergent adverse events leading to dropout *	14 (8.3)	49 (27.4)
Treatment-emergent adverse events leading to dropout (≥2.0%)*		
Nausea	0 (0.0)	14 (7.8)
Dizziness	0 (0.0)	13 (7.3)
Headache	0 (0.0)	7 (3.9)
Fatigue	0 (0.0)	5 (2.8)
Sleep disorder	0 (0.0)	5 (2.8)
Hyperhidrosis	0 (0.0)	4 (2.2)
Serious adverse events*	5 (3.0)	11 (6.1)

*In the main treatment period (24 weeks); Data are numbers of patients (%)

- 73% of the patients in the placebo group and 83% of the patients in the nalmefene group had treatment-emergent adverse events (Table 4); the majority of adverse events were transient, occurred shortly after the first dose, and were of a short duration
- 8.3% of the patients in the placebo group and 27% of the patients in the nalmefene group dropped out due to treatment-emergent adverse events
- 3.0% of the patients in the placebo group and 6.1% of the patients in the nalmefene group had serious adverse events

Conclusions

- In the subgroup of patients with high drinking risk level, nalmefene was superior to placebo; the effect was larger compared to the total population (Mann *et al.* 2012)
- Compared to baseline, total alcohol consumption decreased by approximately 57% in patients receiving nalmefene
- A significantly larger proportion of treatment responders in the nalmefene group than in the placebo group
- Improvements in secondary endpoints CGI, ALAT and GGT, measures not directly derived from alcohol consumption data, were larger in the nalmefene group than in the placebo group
- Nalmefene was safe and well tolerated
- As-needed dosing concept was well accepted and engages patients with alcohol dependence in active and responsible management of their illness
- Nalmefene addresses a public health concern and offers patients with alcohol dependence that are unable to reduce alcohol consumption on their own a new pharmacological treatment paradigm, both in terms of reduction of alcohol consumption as a treatment goal and in terms of dosing regimen

Reference

Mann, K., Bladström, A., Torup, L., Gual, A., van den Brink, W., 2012. Extending the Treatment Options in Alcohol Dependence: A Randomized Controlled Study of As-Needed Nalmefene. *Biol Psychiatry*. Dec 10. pii: S0006-3223(12)00942-0. doi: 10.1016/j.biopsych.2012.10.020. [Epub ahead of print]

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