(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 October 2014 (23.10.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/170353 A1

(51) International Patent Classification:
A61K 31/485 (2006.01) *A61P 25/32* (2006.01)
A61P 25/20 (2006.01)

(21) International Application Number:
PCT/EP2014/057681

(22) International Filing Date:
16 April 2014 (16.04.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2013 00228 17 April 2013 (17.04.2013) DK

(71) Applicant: **H. LUNDBECK A/S** [DK/DK]; Ottiliavej 9, DK-2500 Valby (DK).

(72) Inventors: **MEULIEN, Didier**; 16 rue Heinrich, F-92100 Boulogne Billancourt (FR). **GRUHN, David**; Trekronergade 7A, 3., DK-2500 Valby (DK). **TORUP, Lars**; Inavej 41, DK-3500 Værløse (DK).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2014/170353 A1

(54) Title: NALMEFENE FOR TREATMENT OF PATIENTS WITH SLEEP DISORDER

(57) Abstract: The present invention relates to nalmefene for use in the treatment of sleep disorders. The present invention further relates to nalmefene for use in the treatment of patients with alcohol dependence who have a co-morbid sleep disorder. The invention further relates to nalmefene for use in the reduction of alcohol consumption in said patients. The invention further relates to nalmefene for use in the treatment of sleep disorder in said patients.

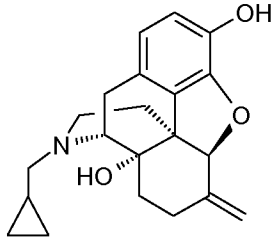
Nalmefene for treatment of patients with sleep disorder

Field of the invention

The present invention relates to nalmefene for use in the treatment of sleep disorders. The present invention further relates to nalmefene for use in the treatment of patients with alcohol dependence who have a co-morbid sleep disorder. The invention further relates to nalmefene for use in the reduction of alcohol consumption in said patients. The invention further relates to nalmefene for use in the treatment of a sleep disorder in said patients.

Background of the invention

Nalmefene [17-(cyclopropylmethyl)-4,5-alpha-epoxy-6-methylenemorphinan-3,14-diol] has the following general formula:



and can be prepared using methods that are well known in the art e.g. starting by manufacturing of naltrexone from noroxymorphone as described in WO 2012/059103 and subsequently manufacturing nalmefene from naltrexone e.g. by the Wittig reaction as described in WO 2010/136039.

Nalmefene is an opioid system modulator with a distinct μ, δ, and κ receptor profile. In vitro studies have demonstrated that nalmefene is a selective opioid receptor ligand with antagonist activity at the μ and δ receptors and partial agonist activity at the κ receptor. Acute alcohol intake was shown to result in mesolimbic dopamine release (facilitated by the release of β-endorphins), which can provide positive reinforcement. Nalmefene is thought to counteract the reinforcement effects and to reduce alcohol consumption, possibly by modulating these cortico-mesolimbic functions.

The efficacy and tolerability of nalmefene in the treatment of alcohol dependence have been evaluated in three phase III studies (two confirmatory 6-month efficacy studies and one 1-year safety study) conducted by Lundbeck (Mann et al. Extending the Treatment Options in Alcohol Dependence: A Randomized Controlled Study of As-Needed Nalmefene. *Biol. Psychiatry* (2013); 73: 706-713; Gual et al. A randomised, double-blind, placebo-controlled, effi-

cacy study of nalmefene, as-needed use, in patients with alcohol dependence. *European Neuropsychopharmacology* (2013); 23(11):1432-1442; van den Brink et al., Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. *J. Psychopharmacol.,* published online before print March 26, 2014, doi: 10.1177/0269881114527362) and 5 studies in alcohol use disorders conducted by the company Biotie (Karhuvaara et al., *Alcohol. Clin. Exp. Res.* 2007; 31: 1179-1187).

A marketing authorisation has recently been granted (February 2013) for oral nalmefene in the European Union (EU) under the tradename Selincro® for the reduction of alcohol consumption in adult patients with alcohol dependence.

Sleep disturbance is one of the most common complaints of alcoholic patients (Zarcone, *Adv. Biosci.* (1978), 21: 29-38). Among community samples, insomnia increases the likelihood of developing alcohol problems. E.g. the Epidemiologic Area Catchment (ECA) study, found that those who reported insomnia in the past year but no psychiatric condition were more than twice as likely to develop alcohol abuse over the subsequent year compared to those without either condition at baseline (Weissman et al., *General Hospital Psychiatry* (1997), 19: 245–250). It has also been found that subjects with chronic alcohol dependence are twice as likely to self-report insomnia as compared with those with no alcohol dependence history (Ford and Kamerow, *JAMA* (1989), 262: 1479–1484; Crum et al., *Alcoholism: Clinical and Experimental Research* (2004), 28: 1533–1540).

Alcohol-dependent patients report difficulties falling asleep (e.g. increased time required to fall asleep), staying asleep (e.g. frequent awakenings) and a decrease in subjective sleep quality associated with daytime fatigue. Many of these subjective sleep complaints are exacerbated during acute withdrawal and also persist during prolonged abstinence, with up to 70% of them still reporting sleep problems that fail to resolve over the course of abstinence. (Brower et al., *Alc. Clin. Exp. Res.* (1998), 22: 1864–1871; Drummond et al., *Alcohol. Clin. Exp. Res.* (1998), 22: 1796–802; Allen et al., *J. Ner. and Ment. Dis.* (1971), 153(6):424-433).

Moreover, poor sleep predicts risk of relapse in recovering alcohol-dependent persons (Brower, *Sleep Med Rev*. (2003), 7: 523–539). It is therefore of particular importance to also treat insomnia since it may interfere with recovery from the primary alcohol addiction and contribute to relapse within the first several months of recovery (Brower et al. *Am J Psychiatry* (2001); 158:399–404; Foster and Peters. *Alcohol Clin. Exp. Res.* (1999), 23: 1044–1051; Brower et al., *Alcoholism: Clinical and Experimental Research* (1998), 22: 1864–1871).

Despite the putative importance of sleep in the recovery process, there is limited information in the addiction literature about appropriate treatment options for insomnia during recovery. This may exist for a variety of reasons: clinicians assume that co-morbid sleep

problems will remit with treatment of the primary alcohol condition; sleep problems are de-emphasized as relatively less important in the early stages of treatment for alcohol dependence; or physicians may be reluctant to address sleep problems due to concerns about sleep medication addiction, withdrawal effects, rebound insomnia, and potential for overdose when mixed with alcohol.(e.g., benzodiazepines and benzodiazepine receptor agonists (BzRAs).

Low doses of sedating tricyclic antidepressants (TCAs), such as amitriptyline and doxepin, are used frequently to treat insomnia. However, their dosing is complicated by alcohol-induced changes in liver metabolism that can result in decreased blood concentrations and efficacy. Another disadvantage is that the tricyclic antidepressants have considerable overdose potential in a population that is prone to suicide. SSRIs, another class of antidepressants, can increase the number of awakenings and worsen sleep in both depressed and non-depressed individuals making them unlikely candidates to treat insomnia. Moreover, studies of alcoholism treatment with TCAs or SSRIs in controlled trials have produced inconsistent results and SSRIs may even worsen drinking outcomes in some patient subgroups. (Arnedt et al. *J. Addict. Dis.* (2007); 26(4): 41–54.)

Therefore, there is a need for new treatments for use in patients with alcohol dependence who have a co-morbid sleep disorder. In particular, there is a need for new treatments which could give rise to advantages such as e.g. improved efficacy and/or a different side effect profile compared to existing treatments.

Summary of the invention

The present invention relates to nalmefene for use in the treatment of a sleep disorder.

In one embodiment, the invention relates to nalmefene for use in the treatment of a patient with alcohol dependence who has a co-morbid sleep disorder.

In one embodiment, the invention relates to nalmefene for use in the reduction of alcohol consumption in a patient with alcohol dependence who has a co-morbid sleep disorder.

In one embodiment, the invention relates to a pharmaceutical composition comprising nalmefene and a second compound, which is a hypnotic agent such as a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine, and optionally acceptable carriers or diluents.

In one embodiment, the invention relates to a kit comprising nalmefene together with a second compound, which is a hypnotic agent such as a benzodiazepine or a benzodiazepine

receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine.

In one embodiment, the invention relates to a method for the treatment of a sleep disorder, which method comprises administering a pharmaceutically acceptable amount of nalmefene to a patient in need thereof.

In one embodiment, the invention relates to a method for reduction of alcohol consumption in a patient with alcohol dependence who has a co-morbid sleep disorder, which method comprises administering a pharmaceutically acceptable amount of nalmefene to said patient.

In one embodiment, the invention relates to a method for reduction of alcohol consumption and for the treatment of a sleep disorder, which method comprises administering a pharmaceutically acceptable amount of nalmefene to a patient in need thereof.

Brief description of drawings

For all figures, -□- = placebo (PBO), -■- = nalmefene (NMF), “B” denotes baseline. Number of patients “N” for placebo (PBO) and nalmefene (NMF), respectively throughout the study is indicated at the X-axis. Patients with and without a sleep disorder at baseline were classified according to their ongoing medical history coded by the Medical Dictionary for Regulatory Activities (MedDRA).

Figures 1-2 show the change from baseline in monthly Heavy Drinking days (HDDs) and Total Alcohol Consumption (TAC) (g/day) in patients with a sleep disorder at baseline vs. patients without a sleep disorder at baseline.

Figures 1a-1b show the change from baseline in monthly HDDs. X-axis: time (months); Y-axis: change from baseline in mean HDD.

Figure 1a: Patients without a sleep disorder at baseline, change in monthly HDD.

Figure 1b: Patients with a sleep disorder at baseline, change in monthly HDD.

Figures 2a-2b show the change from baseline in monthly TAC (g/day). X-axis: time (months); Y-axis: change from baseline in mean TAC.

Figure 2a: Patients without a sleep disorder at baseline, change in monthly TAC.

Figure 2b: Patients with a sleep disorder at baseline, change in monthly TAC.

Figures 3-9 indicate change from baseline in POMS scores in patients with a sleep disorder at baseline vs. patients without a sleep disorder at baseline. X-axis: time (weeks); Y-axis: change from baseline in mean POMS.

Figure 3a. Patients without a sleep disorder at baseline, change in POMS total mood disturbance (TMD).
Figure 3b: Patients with a sleep disorder at baseline, change in POMS total mood disturbance (TMD).
Figure 4a. Patients without a sleep disorder at baseline, change in POMS Tension-Anxiety.
Figure 4b: Patients with a sleep disorder at baseline, change in POMS Tension-Anxiety.
Figure 5a. Patients without a sleep disorder at baseline, change in POMS Depression-Rejection.
Figure 5b: Patients with a sleep disorder at baseline, change in POMS Depression-Rejection.
Figure 6a. Patients without a sleep disorder at baseline, change in POMS Anger-Hostility.
Figure 6b: Patients with a sleep disorder at baseline, change in POMS Anger-Hostility.
Figure 7a. Patients without a sleep disorder at baseline, change in POMS Vigour.
Figure 7b: Patients with a sleep disorder at baseline, change in POMS Vigour.
Figure 8a. Patients without a sleep disorder at baseline, change in POMS Fatigue.
Figure 8b: Patients with a sleep disorder at baseline, change in POMS Fatigue.
Figure 9a. Patients without a sleep disorder at baseline, change in POMS Confusion.
Figure 9b: Patients with a sleep disorder at baseline, change in POMS Confusion.

Definitions

Throughout the description, the term “nalmefene” is intended to include any form of the compound, such as the free base and pharmaceutically acceptable salts. The free base and pharmaceutically acceptable salts include anhydrous forms and solvated forms such as hydrates. The anhydrous forms and the solvates include amorphous and crystalline forms. In a particular embodiment, nalmefene is in the form of a hydrochloride salt. In a more particular embodiment, nalmefene is in the form of the hydrochloride dihydrate. Throughout the application, when a dose is specified for nalmefene, said dose is calculated as the free base, i.e. when the nalmefene dose is 18 mg this corresponds to 18 mg of nalmefene free base.

In the present context, the term “total alcohol consumption” abbreviated TAC indicates average total alcohol consumption measured in g/day.

In the present context, the term “heavy drinking day” abbreviated HDD indicates a day with a total alcohol consumption ≥60 g for men and ≥40 g for women.

In the present context, “as-needed dosing” indicates that on each day a patient perceives a risk of drinking alcohol, one dose of nalmefene should be taken, preferably 1-2 hours

prior to the anticipated time of drinking. If the patient has started drinking alcohol without taking nalmefene, the patient should take one tablet as soon as possible after that.

As used herein, the term “drinking risk level” abbreviated DRL is defined according to the criterias defined by the World Health Organization in *“International Guide for Monitoring Alcohol Consumption and Related Harm”* (2000), WHO, as outlined in Table 1 below.

Table 1: WHO Drinking Risk Levels (DRLs) of Alcohol Consumption

DRL	Total Alcohol Consumption (g/day)	
	Men	Women
Very high risk	>100	>60
High risk	>60 to 100	>40 to 60
Medium risk	>40 to 60	>20 to 40
Low risk	1 to 40	1 to 20

Drinking Risk Levels according to Table 1 can be assessed e.g. by calculating mean daily alcohol consumption in g/day over a period such as 1 week or longer, such as 2 weeks or longer, such as 3 weeks or longer, such as 4 weeks or longer, such as 1 month or longer such as 2 months or longer, such as 3 months or longer, such as 4 months or longer, such as 5 months or longer, such as 6 months or longer, such as about 1 year. Assessment of DRL can be performed by specialists and/or physicians such as general practitioners and/or other health care providers based on patients estimates of their alcohol consumption.

Throughout the application, the term “high risk” or “at least high risk” is intended to include the two groups defined as “high risk” and “very high risk” according to WHOs drinking risk levels listed in Table 1, i.e. patients having drinking risk level corresponding to a total alcohol consumption of >60 g/day of pure alcohol for men and >40 g/day for women. The present invention does not distinguish between patients with high and very high drinking risk levels, and when the terms “high drinking risk level” or “high DRL” are used in a claim or in an embodiment of the invention it is intended to include both the group defined as “high risk” and the group defined as “very high risk” according to WHOs drinking risk levels listed in Table 1.

As used herein, the terms “motivational support” and “counselling focused on enhanced treatment adherence and reduced alcohol consumption” indicate psychological motivation-enhancing interventions and can be used interchangeably with the terms “psychosocial support” or “psychosocial intervention focused on treatment adherence and reducing alcohol consumption”. Said motivational support can be administered by a specialist and/or a physician such as a general practitioner and/or other health care providers. One example of such

interventions is the BRENDA model, which is a time-limited, patient-centered clinical motivational intervention that complements the use of medication with focus on changing behavior and increasing medication adherence. The BRENDA model has been described by Starosta et al., *J. Psychiatr. Pract.* (2006), Vol. 12(2): 80-89, the entire contents of which are incorporated herein by reference. The term “initial motivational support” indicates such motivation-enhancing interventions provided to the patient prior to treatment with nalmefene. The term “ongoing motivational support” indicates such motivation-enhancing interventions provided to the patient concurrent to treatment with nalmefene e.g. on a recurrent basis.

In the present context, “Pharmaceutical composition” refers to a dose form such as an oral dose form, such as a solid oral dose form, typically tablets or capsules. “Pharmaceutical compositions of the present invention” refers to all pharmaceutical compositions covered by the claims and description.

In the present context, a “unit dosage form” refers to a formulation unit of a pharmaceutical composition e.g. one tablet or capsule.

In the present context, “therapeutically effective amount” of a compound means the amount/dose of a compound or pharmaceutical composition that is sufficient to produce an effective response (i.e., a biological or medical response of a tissue, system, animal or human sought by a researcher, veterinarian, medical doctor or other clinician) upon administration to a patient. The "therapeutically effective amount" will vary depending on, inter alia, the disease and its severity, and on the age, weight, physical condition and responsiveness of the patient to be treated. Furthermore, the "therapeutically effective amount" may vary if nalmefene is combined with one or more compounds: In such a case the amount of a given compound might be lower, such as a sub-effective amount.

In the present context, "treatment" and "treating" refers to the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relieve the symptoms and complications, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. In one aspect of the present invention, “treatment” and “treating” refers to prophylactic (preventive) treatment. In another aspect, “treatment and “treating” re-

fers to curative treatment. The patient to be treated is preferably a mammal, in particular a human being.

The term “alcohol dependence” is a commonly known term for a skilled person and is e.g. described in the revised 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition text revision, American Psychiatric Publishing, 2000). As used herein, the term “alcohol dependence” is defined as the presence of three or more of the seven areas of life impairment related to alcohol in the same 12-month period. These impairments include 1) tolerance, 2) withdrawal, 3) the alcohol is often taken in larger amounts or over a longer period than was intended, 4) persistent desire or unsuccessful efforts to cut down or control alcohol intake, 5) a great deal of time is spent in activities necessary to obtain alcohol, intake alcohol, or recover from its effects, 6) important social, occupational, or recreational activities are given up or reduced because of alcohol consumption, 7) alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol consumption.

The term “sleep disorder” is described in DSM-IV-TR and refers to a variety of conditions characterized by a disturbance in sleep as the main feature. In the present context, sleep disorders include Primary Insomnia, Primary Hypersomnia, Narcolepsy, Breathing-Related Sleep Disorder, Circadian Rhythm Sleep Disorder, Dyssomnia Not Otherwise Specified, Nightmare Disorder, Sleep Terror Disorder, Sleepwalking Disorder, Parasomnia Not Otherwise Specified.

In the present context, “patients with co-morbid sleep disorder” refers to patients who are alcohol dependent and at the same time have a sleep disorder. In one embodiment, said sleep disorder is caused by said alcohol dependence e.g. said sleep disorder is an alcohol-induced sleep disorder. In one embodiment, said alcohol dependence is caused by said sleep disorder. In one embodiment said alcohol dependence and said sleep disorder are not causally related to each other.

The term “alcohol induced sleep disorder” is described in DSM-IV-TR and refers to a disorder characterized by prominent sleep disturbance directly due to concurrent use, or recent discontinuation of use of alcohol or that alcohol use is etiologically related to the sleep disturbance.

The term “POMS” is an abbreviation of “profile of mood states” and refers to a self-report inventory scale developed to assess the effect of e.g. new medication on mood states and mood changes. The scale measures six domains: Tension-Anxiety, Depression-Rejection, Anger-Hostility, Vigour-Activity, Fatigue-Inertia, and Confusion-Bewilderment. A

total mood disturbance (TMD) score can be calculated. In general, a lower POMS score indicates a better mood state than a higher score except for vigour-activity, for which a higher POMS score indicates a better mood state. The scale has been described e.g. by McNair et al., *Profile of mood states*. San Diego, CA: Educational and Industrial Testing Service and by Nyenhios and Yamamoto, *J.Clin.Psychology,* (1999), Vol. 55(1): 79-86.

"MedDRA" is an abbreviation of Medical Dictionary for Regulatory Activities which is a clinically validated international medical terminology dictionary (and thesaurus) used by regulatory authorities in the pharmaceutical industry during the regulatory process, from pre-marketing to post-marketing activities, and for data entry, retrieval, evaluation, and presentation. In addition, it is the adverse event classification dictionary endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Detailed description of the invention

The efficacy of nalmefene in the reduction of alcohol consumption in patients with alcohol dependence (DSM-IV) has been evaluated in studies 12014A, 12023A and 12013A. The efficacy of nalmefene was measured using two co-primary endpoints: the change from baseline to month 6 in the monthly number of heavy drinking days (HDDs) and the change from baseline to month 6 in the average daily total alcohol consumption (TAC). In the total patient group, nalmefene was superior to placebo in reducing the number of HDDs and in reducing TAC.

The inventors have found that nalmefene significally reduced the alcohol consumption in patients with a sleep disorder at baseline. In patients with a sleep disorder at baseline as well as in patients without sleep disorders at baseline, there was a decrease in reducing the number of HDDs at month 6 with nalmefene although there was no difference to placebo at month 6 in patients with a sleep disorder at baseline. However in the patients with a sleep disorder at baseline the effect of nalmefene on HDD was already evident at month 1 with differences to placebo at month 1 and throughout month 4. Furthermore, in patients with a sleep disorder at baseline, the effect of nalmefene on TAC at month 6 was more pronounced compared to placebo than in patients without a sleep disorder at baseline. I.e. overall nalmefene is effective in reducing alcohol consumption in patients with a sleep disorder at baseline (Figures 1-2). Therefore, in one embodiment, the present invention relates to nalmefene for use in the treatment of patients with alcohol dependence who have a co-morbid sleep disorder. In one embodiment, the present invention relates to nalmefene for use

in the reduction of alcohol consumption in patients with alcohol dependence who have a co-morbid sleep disorder.

Assessment of POMs scores in studies 12014A, 12023A and 12013A was used to evaluate the effect of nalmefene on mood states and mood changes throughout the study. The inventors of the present invention surprisingly found that nalmefene has an effect on the POMS scores in patients with a sleep disorder. Tables 3 and 5 indicate that patients with a sleep disorder at baseline had higher POMS scores at baseline when compared to those without sleep disorders. The change in POMS scores from baseline are illustrated in Figures 3-9. Figures 3a-9a indicates that in patients without a sleep disorder at baseline, the pattern in POMS score was stabile throughout the study with no pronounced difference between nalmefene and placebo. Figures 3b-9b indicates that patients with a sleep disorder at baseline who received nalmefene had a better POMS score at the end of the study than the patients with a sleep disorder at baseline who received placebo. In particular Figures 3b, 4b, 5b, 6b, 7b and 8b representing total sleep disturbance, tension-anxiety, depression-rejection, anger-hostility vigour and fatigue, respectively, indicates better POMS scores in weeks 4-24 in patients who received nalmefene compared to patients who received placebo. Overall, the POMS data indicates that the general mood state improves in patients with sleep disorder when they are treated with nalmefene.

Accordingly, in one embodiment, the present invention therefore relates to nalmefene for treatment of a sleep disorder. In one embodiment, the invention relates to nalmefene for treatment of a sleep disorder in patients with alcohol dependence who have a co-morbid sleep disorder. In a further embodiment, the invention relates to nalmefene for use in the reduction of alcohol consumption and for treatment of a sleep disorder in patients with alcohol dependence who have a co-morbid sleep disorder.

In one embodiment, nalmefene is used as the sole active ingredient for the treatment of a sleep disorder. In one embodiment, nalmefene is used as the sole active ingredient in the treatment of patients with alcohol dependence who have a co-morbid sleep disorder.

In one embodiment, nalmefene is used in combination with a second compound, which is a hypnotic agent such as a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine, for the treatment of a sleep disorder. In another embodiment, nalmefene is used in combination with a second compound, which is a hypnotic agent such as a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic;

or an antihistamine, in the treatment of patients with alcohol dependence who have a co-morbid sleep disorder.

The present invention also relates to a pharmaceutical composition comprising nalmefene and a second compound, which is a hypnotic agent such as a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine, and optionally acceptable carriers or diluents.

Further assessment of the effect of nalmefene on the treatment of sleep disorders can be performed by testing nalmefene in one or more non-clinical models e.g. such as in rat sleep profiling using electroencephalogram (EEG) recordings, as outlined in Example 4. In such models nalmefene can be tested as the sole active substance as well as in combination with other compounds.

According to the present invention, nalmefene or a pharmaceutically acceptable salt thereof may be administered in any suitable way, e.g. orally, transmucosally or parenterally, and it may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. In another embodiment, and in accordance with the purpose of the present invention, nalmefene is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a suspension, solution or dispersion for injection. Additionally, nalmefene may be administered with a pharmaceutically acceptable carrier, such as an adjuvant and/or diluent.

Methods for the preparation of solid or liquid pharmaceutical preparations are well known in the art. See e.g. Remington: The Science and Practice of Pharmacy, 21st ed., Lippincott Williams & Wilkins (2005). Tablets may thus be prepared by mixing the active ingredients with an ordinary carrier, such as an adjuvant and/or diluent, and subsequently compressing the mixture in a tableting machine. Non-limiting examples of adjuvants and/or diluents include: corn starch, lactose, talcum, magnesium stearate, gelatin, lactose, gums, and the like. Any other adjuvant or additive such as colorings, aroma, and preservatives may also be used provided that they are compatible with the active ingredients. The pharmaceutical compositions of the invention thus typically comprise an effective amount of nalmefene and one or more pharmaceutically acceptable carrier. A suitable oral formulation of nalmefene is described in WO 2012/059103.

Without limiting the invention in any way, it is intended that any one of the aspects or embodiments of this patent application is suitable for the medicaments or pharmaceutical compositions described herein.

Nalmefene may be administered as an oral dose form, such as a solid oral dose form, typically tablets or capsules, or as a liquid oral dose form. Nalmefene may be administered in an immediate release dosage form or a controlled or sustained release dosage form. Nalmefene may be conveniently administered orally in unit dosage forms, such as tablets or capsules, containing the active ingredient in an amount from about 1 to about 100 mg, such as from 5 to 50 mg. Typically, the pharmaceutical composition comprises from 10 mg to 20 mg, such as about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg or about 20 mg of nalmefene. In a preferred embodiment, the pharmaceutical composition comprises about 18 mg of nalmefene. In one embodiment, the unit dosage form comprises nalmefene in a therapeutically effective amount.

In one embodiment, nalmefene is taken as-needed, that is, on each day a patient perceives a risk of drinking alcohol, one dose of nalmefene should be taken, preferably 1-2 hours prior to anticipated time of drinking. In one embodiment, if the patient has started drinking alcohol without taking nalmefene, the patient should take one dose of nalmefene as soon as possible after that.

Nalmefene according to the present invention is intended to be used for dosing in humans who are adults or adolescents.

In one embodiment, nalmefene is in the form of the hydrochloride dihydrate.

According to the invention, nalmefene can be used in combination with a second compound which is a hypnotic agent such as a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine. Said benzodiazepine or benzodiazepine receptor agonist may e.g. be selected from the following compounds; diazepam, chlordiazepoxid, clonazepam, bromazepam, estazolam, oxazepam, flurazepam, flunitrazepam, temazepam, triazolam, zolpidem, zaleplon, and eszopiclone. Said anticonvulsant may e.g. be selected from the following compounds; carbamazepine and gabapentin. Said sedating tricyclic or tetracyclic antidepressant may e.g. be selected from the following compounds; amitriptyline, doxepin, mirtazapin trazodone, or nefazodone. Said melatonin agonist may e.g. be selected from melatonin, ramelteon and agomelatine. Said sedating antipsychotic may e.g. be selected from haloperidol and quetiapine. Said antihistamine may e.g. be selected from diphenhydramine and doxylamine. The compounds mentioned above may be used in the form of the base or a pharmaceutically acceptable salt, such as an acid addition salt, thereof. The above list of hypnotic agents may not be construed as limiting.

Hypnotic agents including the compounds specifically mentioned hereinabove, differ both in molecular weight and in activity. As a consequence, the amount of said second compound used in combination therapy depends on the nature of said second compound. In one embodiment of the invention, said second compound is administered at lower doses than required when the compound is used alone. In another embodiment, said second compound is administered in normal therapeutic doses.

To prepare the pharmaceutical compositions of this invention, an appropriate amount of the active ingredient(s), in salt form or base form, is combined in an intimate admixture with a pharmaceutically acceptable carrier, which can take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable for administration orally, rectally, percutaneously or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. As used in the specification and claims, unit dosage form refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient(s) calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Nalmefene may be administered before, during or after the administration of said second compound provided that the time between the administration of nalmefene and the administration of said second compound is such that ingredients are allowed to act synergistically on the CNS. When simultaneous administration of nalmefene and said second compound is envisaged, a composition containing both said second compound and nalmefene may be particularly convenient. Alternatively, nalmefene and said second compound may be administered separately in the form of suitable compositions. The compositions may be prepared as described hereinabove.

The present invention also comprises products containing nalmefene and a second compound, which is a hypnotic agent such as a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine, as a combination preparation for simultaneous, separate or sequential use in psychiatric drug therapy. Such products may comprise, for example, a kit comprising discrete unit dosage forms containing nalmefene and discrete unit dosage forms containing a sleep agent, all contained in the same container or pack, e.g. a blister pack.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein (to the maximum extent permitted by law), regardless of any separately provided incorporation of particular documents made elsewhere herein.

The use of the terms “a” and “an” and “the” and similar referents in the context of describing the invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. For example, the phrase "the compound" is to be understood as referring to various "compounds" of the invention or particular described aspect, unless otherwise indicated.

The description herein of any aspect or aspect of the invention using terms such as “comprising”, “having,” “including,” or “containing” with reference to an element or elements is intended to provide support for a similar aspect or aspect of the invention that “consists of”, “consists essentially of”, or “substantially comprises” that particular element or elements, unless otherwise stated or clearly contradicted by context (e.g., a composition described herein as comprising a particular element should be understood as also describing a composition consisting of that element, unless otherwise stated or clearly contradicted by context).

It should be understood that the various aspects, embodiments, implementations and features of the invention mentioned herein may be claimed separately, or in any combination.

Embodiments according to the invention

In the following, embodiments of the invention are disclosed. The first embodiment is denoted E1, the second embodiment is denoted E2 and so forth.

E1. Nalmefene for use in the treatment of a sleep disorder.

E2. Nalmefene for use in the treatment of a patient with alcohol dependence who has a co-morbid sleep disorder.

E3. Nalmefene for use in the reduction of alcohol consumption in a patient with alcohol dependence who has a co-morbid sleep disorder.

E4. Nalmefene according to embodiment 1 or 2 for use in the treatment of a sleep disorder in a patient with alcohol dependence who has a co-morbid sleep disorder.

E5. Nalmefene for use in the reduction of alcohol consumption according to embodiment 3 and for use in the treatment of a sleep disorder according to embodiment 4 in a patient with alcohol dependence who has a co-morbid sleep disorder.

E6. Nalmefene according to any of embodiments 1-5, wherein said sleep disorder or co-morbid sleep disorder is an alcohol induced sleep disorder.

E7. Nalmefene according to any of embodiments 2-5, wherein said alcohol dependence is caused by said sleep disorder.

E8. Nalmefene according to any of embodiments 2-5, wherein said alcohol dependence and said sleep disorder are not causally related to each other.

E9. Nalmefene according to any of embodiments 1-8, wherein said sleep disorder or co-morbid sleep disorder is selected from Primary Insomnia, Primary Hypersomnia, Narcolepsy, Breathing-Related Sleep Disorder, Circadian Rhythm Sleep Disorder, Dyssomnia Not Otherwise Specified, Nightmare Disorder, Sleep Terror Disorder, Sleepwalking Disorder, Parasomnia Not Otherwise Specified.

E10. Nalmefene according to any of embodiments 1-9, wherein said nalmefene is the sole active ingredient used in the treatment of said sleep disorder and/or in the reduction of said alcohol consumption.

E11. Nalmefene according to any of embodiments 1-9, wherein said patient is further treated with a second compound which is a hypnotic agent selected from a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or

tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine.

E12. Nalmefene according to embodiment 11, wherein said second compound is a benzodiazepine or a benzodiazepine receptor agonist.

E13. Nalmefene according to embodiment 12, wherein said benzodiazepine or benzodiazepine receptor agonist is selected from diazepam, chlordiazepoxid, clonazepam, bromazepam, estazolam, oxazepam, flurazepam, flunitrazepam, temazepam, triazolam, zolpidem, zaleplon, and eszopiclone or a pharmaceutically acceptable salt of any of these compounds.

E14. Nalmefene according to embodiment 11, wherein said second compound is an anticonvulsant.

E15. Nalmefene according to embodiment 14, wherein said anticonvulsant is selected from carbamazepine and gabapentin or a pharmaceutically acceptable salt of any of these compounds.

E16. Nalmefene according to embodiment 11, wherein said second compound is a sedating tricyclic or tetracyclic antidepressant.

E17. Nalmefene according to embodiment 16, wherein said sedating tricyclic or tetracyclic antidepressant is selected from amitriptyline, doxepin, mirtazapine, trazodone and nefazodone or a pharmaceutically acceptable salt of any of these compounds.

E18. Nalmefene according to embodiment 11, wherein said second compound is a melatonin agonist.

E19. Nalmefene according to embodiment 18, wherein said melatonin agonist is selected from melatonin, ramelteon and agomelatine or a pharmaceutically acceptable salt of any of these compounds.

E20. Nalmefene according to embodiment 11, wherein said second compound is a sedating antipsychotic.

E21. Nalmefene according to embodiment 20, wherein said sedating antipsychotic is selected from haloperidol and quetiapine or a pharmaceutically acceptable salt of any of these compounds.

E22. Nalmefene according to embodiment 11, wherein said second compound is an antihistamine.

E23. Nalmefene according to embodiment 22, wherein said antihistamine is selected from diphenhydramine and doxylamine or a pharmaceutically acceptable salt of any of these compounds.

E24. Nalmefene according to any of embodiments 11-23, wherein said nalmefene and said second compound are contained in the same unit dosage form.

E25. Nalmefene according to any of embodiments 11-23, wherein said nalmefene and said second compound are contained in the separate unit dosage forms.

E26. Nalmefene according to any of embodiments 2-25, wherein said patient has at least a medium drinking risk level.

E27. Nalmefene according to embodiment 26, wherein said patient has a high drinking risk level.

E28. Nalmefene according to embodiment 27, wherein said patient has a drinking risk level corresponding to consumption >60 g/day of pure alcohol for men and >40 g/day for women.

E29. Nalmefene according to any of embodiments 1-28, wherein said nalmefene is to be used as-needed.

E30. Nalmefene according to any of embodiments 1-29, wherein said nalmefene is used in a dose of 10-20 mg such as 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg or 20 mg.

E31. Nalmefene according to embodiment 30, wherein said nalmefene is used in a dose of 18 mg.

E32. Nalmefene according to any of embodiments 1-31, wherein said nalmefene is used in the form of a pharmaceutically acceptable acid addition salt.

E33. Nalmefene according to embodiment 32, wherein said nalmefene is used in the form of a hydrochloride salt.

E34. Nalmefene according to embodiment 33, wherein said nalmefene is used in the form of the hydrochloride dihydrate.

E35. Nalmefene according to embodiment 34, wherein said nalmefene is used in a crystalline form.

E36. Nalmefene according to any of embodiments 1-35, wherein said nalmefene is contained in an oral dose form such as tablets or capsules.

E37. A pharmaceutical composition comprising nalmefene and a second compound which is a hypnotic agent selected from a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine, and optionally acceptable carriers or diluents.

E38. A kit comprising nalmefene together with a second compound which is a hypnotic agent selected from a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine.

E39. The pharmaceutical composition according to embodiment 37 or the kit according to embodiment 39, wherein said second compound is a benzodiazepine or a benzodiazepine receptor agonist.

E40. The pharmaceutical composition or the kit according to embodiment 39, wherein said benzodiazepine or benzodiazepine receptor agonist is selected from diazepam, chlor-

diazepoxid, clonazepam, bromazepam, estazolam, oxazepam, flurazepam, flunitrazepam, temazepam, triazolam, zolpidem, zaleplon, and eszopiclone or a pharmaceutically acceptable salt of any of these compounds.

E41. The pharmaceutical composition according to embodiment 37 or the kit according to embodiment 38, wherein said second compound is an anticonvulsant.

E42. The pharmaceutical composition or the kit according to embodiment 41, wherein said anticonvulsant is selected from carbamazepine and gabapentin or a pharmaceutically acceptable salt of any of these compounds.

E43. The pharmaceutical composition according to embodiment 37 or the kit according to embodiment 38, wherein said second compound is a sedating tricyclic or tetracyclic antidepressant.

E44. The pharmaceutical composition or the kit according to embodiment 43, wherein said sedating tricyclic or tetracyclic antidepressant is selected from amitriptyline, doxepin, mirtazapine, trazodone and nefazodone or a pharmaceutically acceptable salt of any of these compounds.

E45. The pharmaceutical composition according to embodiment 37 or the kit according to embodiment 38, wherein said second compound is a melatonin agonist.

E46. The pharmaceutical composition or the kit according to embodiment 45, wherein said melatonin antagonist is selected from melatonin, ramelteon and agomelatine or a pharmaceutically acceptable salt of any of these compounds.

E47. The pharmaceutical composition according to embodiment 37 or the kit according to embodiment 38, wherein said second compound is a sedating antipsychotic.

E48. The pharmaceutical composition or the kit according to embodiment 47, wherein said sedating antipsychotic is selected from haloperidol and quetiapine or a pharmaceutically acceptable salt of any of these compounds.

E49. The pharmaceutical composition according to embodiment 37 or the kit according to embodiment 38, wherein said second compound is an antihistamine.

E50. The pharmaceutical composition or the kit according to embodiment 49, wherein said antihistamine is selected from diphenhydramine and doxylamine or a pharmaceutically acceptable salt of any of these compounds.

E51. The kit according to any of embodiments 38-50, which is adapted for sequential administration of said nalmefene and said second compound.

E52. The pharmaceutical composition or the kit according to any of embodiments 37-50, which is adapted for simultaneous administration of said nalmefene and said second compound.

E53. The pharmaceutical composition or the kit according to embodiment 52, wherein said nalmefene and said second compound are contained in the same unit dosage form.

E54. The pharmaceutical composition or the kit according to any of embodiments 37-53, wherein said nalmefene is present in a dose of 10-20 mg such as 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg or 20 mg.

E55. The pharmaceutical composition or the kit according to embodiment 54, wherein said nalmefene is present in a dose of 18 mg.

E56. The pharmaceutical composition or the kit according to any of embodiments 37-55, wherein said nalmefene is present in the form of a pharmaceutically acceptable acid addition salt.

E57. The pharmaceutical composition or the kit according to embodiment 56, wherein said nalmefene is present in the form of a hydrochloride salt.

E58. The pharmaceutical composition or the kit according to embodiment 57, wherein said nalmefene is present in the form of the hydrochloride dihydrate.

E59. The pharmaceutical composition or the kit according to embodiment 58, wherein said nalmefene is present in a crystalline form.

E60. A method for the treatment of a sleep disorder, which method comprises administering a pharmaceutically acceptable amount of nalmefene to a patient in need thereof.

E61. A method for reduction of alcohol consumption in a patient with alcohol dependence who has a co-morbid sleep disorder, which method comprises administering a pharmaceutically acceptable amount of nalmefene to said patient.

10

E62. The method according to embodiment 60, wherein said patient is alcohol dependent and has a co-morbid sleep disorder.

E63. A method for reduction of alcohol consumption and for the treatment of a sleep disorder, which method comprises administering a pharmaceutically acceptable amount of nalmefene to a patient in need thereof.

E64. The method according to embodiment 63, wherein said patient is alcohol dependent and has a co-morbid sleep disorder.

20

E65. The method according to any of embodiments 60-64, wherein said sleep disorder or co-morbid sleep disorder is an alcohol induced sleep disorder.

E66. The method according to any of embodiments 61-64, wherein said alcohol dependence is caused by said sleep disorder.

E67. The method according to any of embodiments 61-64, wherein said said alcohol dependence and said sleep disorder are not causally related to each other.

30 E68. The method according to any of embodiments 60-67, wherein said sleep disorder or co-morbid sleep disorder is selected from Primary Insomnia, Primary Hypersomnia, Narcolepsy, Breathing-Related Sleep Disorder, Circadian Rhythm Sleep Disorder, Dyssomnia Not Otherwise Specified, Nightmare Disorder, Sleep Terror Disorder, Sleepwalking Disorder, Parasomnia Not Otherwise Specified.

E69. The method according to any of embodiments 60-68, wherein said nalmefene is the sole active ingredient used in the treatment of said sleep disorder and/or in the reduction of said alcohol consumption.

E70. The method according to any of embodiments 60-68, which method further comprises administering a pharmaceutically acceptable amount of a second compound which is a hypnotic agent selected from a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine.

E71. The method according to embodiment 70, wherein said second compound is a benzodiazepine or a benzodiazepine receptor agonist.

E72. The method according to embodiment 71, wherein said benzodiazepine or benzodiazepine receptor agonist is selected from diazepam, chlordiazepoxid, clonazepam, bromazepam, estazolam, oxazepam, flurazepam, flunitrazepam, temazepam, triazolam, zolpidem, zaleplon, and eszopiclone or a pharmaceutically acceptable salt of any of these compounds.

E73. The method according to embodiment 70, wherein said second compound is an anticonvulsant.

E74. The method according to embodiment 73, wherein said anticonvulsant is selected from carbamazepine and gabapentin or a pharmaceutically acceptable salt of any of these compounds.

E75. The method according to embodiment 70, wherein said second compound is a sedating tricyclic or tetracyclic antidepressant.

E76. The method according to embodiment 75, wherein said sedating tricyclic or tetracyclic antidepressant is selected from amitriptyline, doxepin, mirtazapine, trazodone and nefazodone or a pharmaceutically acceptable salt of any of these compounds.

E77. The method according to embodiment 70, wherein said second compound is a melatonin agonist.

E78. The method according to embodiment 77, wherein said melatonin agonist is selected from melatonin, ramelteon and agomelatine or a pharmaceutically acceptable salt of any of these compounds.

E79. The method according to embodiment 70, wherein said second compound is a sedating antipsychotic.

E80. The method according to embodiment 79, wherein said sedating antipsychotic is selected from haloperidol and quetiapine or a pharmaceutically acceptable salt of any of these compounds.

E81. The method according to embodiment 70, wherein said second compound is an antihistamine.

E82. The method according to embodiment 81, wherein said antihistamine is selected from diphenhydramine and doxylamine or a pharmaceutically acceptable salt of any of these compounds.

E83. The method according to any of embodiments 70-82, wherein said nalmefene and said second compound are contained in the same unit dosage form.

E84. The method according to any of embodiments 70-82, wherein said nalmefene and said second compound are contained in separate unit dosage forms.

E85. The method according to any of embodiments 61-84, wherein said patient has at least a medium drinking risk level.

E86. The method according to embodiment 85, wherein said patient has a high drinking risk level.

E87. The method according to embodiment 86, wherein said patient has a drinking risk level corresponding to consumption >60 g/day of pure alcohol for men and >40 g/day for women.

E88. The method according to any of embodiments 60-87, wherein said nalmefene is administered as-needed.

E89. The method according to any of embodiments 60-87, wherein said nalmefene is administered in a dose of 10-20 mg such as 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg or 20 mg.

E90. The method according to embodiment 89, wherein said nalmefene is administered in a dose of 18 mg.

E91. The method according to any of embodiments 60-90, wherein said nalmefene is administered in the form of a pharmaceutically acceptable acid addition salt.

E92. The method according to embodiment 91, wherein said nalmefene is administered in the form of a hydrochloride salt.

E93. The method according to embodiment 92, wherein said nalmefene is administered in the form of the hydrochloride dihydrate.

E94. The method according to embodiment 93, wherein said nalmefene is administered in a crystalline form.

E95. The method according to any of embodiments 60-94, wherein said nalmefene is contained in an oral dose form such as tablets or capsules.

Examples

The invention will be illustrated by the following non-limiting examples.

Clinical assessment

The diagnosis of alcohol dependence was based on the DSM-IV-TR criteria. For this purpose, the investigator interviewed the patient in a structured way by using the Mini International Neuropsychiatric Interview (MINI) standardized interview (Lecrubier et al. The Mini International Neuropsychiatric Interview (M.I.N.I.). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiat.* (1997), 12: 224-31). The M.I.N.I.

is designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV. Its use permits a standardised assessment of the diagnostic criteria. The M.I.N.I. interview was used at the screening visit. Clinicians used it after a training session. The M.I.N.I. approach can also be used to select patients with a sleep disorder at baseline.
Another approach to identify patients with a sleep disorder is by defining sleep Disorder at baseline as any ongoing medical history coded by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term as 'Sleep Disorder', 'Poor Quality Sleep', 'Somanambulism' and/or any term including 'Insomnia'. In examples 1 and 2 below patients classified with a sleep disorder at baseline was selected based on said MedDRA terms.

Example 1: Clinical efficacy on the reduction of alcohol consumption

The efficacy of nalmefene on the reduction of alcohol consumption in patients with alcohol dependence (DSM-IV) was evaluated in two efficacy studies (Study 12014A and Study 12023A) and a safety study (Study 12013A). All studies were multi-national, multi-site, randomised, double blind, two parallel group, placebo controlled studies. The efficacy was evaluated over 24 weeks of treatment. The studies included outpatients, aged ≥18 years, with a primary diagnosis of alcohol dependence. A patient was eligible for participation in the study if, in the 4 weeks preceding the Screening Visit, he/she had: ≥6 HDDs, ≤14 consecutive abstinent days, did not have serum aspartate aminotransferase (ASAT) and/or serum alanine aminotransferase (ALAT) values >3 times upper limit of the reference range, that are in the investigator's opinion clinically significant. Patients with psychiatric co-morbidity (that is, patients who used stable doses of antipsychotics and/or certain antidepressants) were also included unless the treatment of the psychiatric comorbidity had to take priority over treatment of the drinking problem, or was likely to interfere with study treatment or impairs treatment compliance.

The studies included in total 1997 patients, 1173 of whom were treated with nalmefene 18 mg in an as-needed dosing regimen. A motivational and adherence enhancing intervention was administered to all the patients to support the patients in changing their behavior and to enhance adherence to treatment.

The efficacy of nalmefene on the reduction of alcohol consumption was measured using two co-primary endpoints: the change in the monthly number of heavy drinking days (HDDs) and the change in the average daily total alcohol consumption (TAC). A HDD was defined as a day with a consumption ≥ 60 g alcohol for men and ≥ 40 g for women.

The change in HDD and TAC over time in patients treated with nalmefene or placebo is reflected in Figures 1-2 indicating that nalmefene is effective in reducing alcohol consumption in patients with a sleep disorder at baseline.

Example 2: Clinical efficacy measured by POMS score.

Assessment of POMs scores in Studies 14014A, 12023A and 12013A described above was used to evaluate the effect of nalmefene on mood states and mood changes throughout the study. The change in POMS scores from baseline are illustrated in Figures 3-9. Figures 3a-9a indicates that in patients without a sleep disorder at baseline, the pattern in POMS score was stabile throughout the study with no pronounced difference between nalmefene and placebo.

Tables 3 and 5 indicate that patients with a sleep disorder at baseline had higher POMS scores at baseline when compared to those without a sleep disorder. Figures 3b-9b indicates that the patients with a sleep disorder at baseline who received nalmefene had a better POMS score at the end of the study than the patients with a sleep disorder at baseline who received placebo. In particular Figures 3b, 4b, 5b, 6b, 7b and 8b representing total sleep disturbance, tension-anxiety, depression-rejection, anger-hostility, vigour and fatigue, respectively, indicates better POMS scores in weeks 4-24 in patients who received nalmefene compared to patients who received placebo. In general a lower POMS score indicates a better mood state than a higher score except for vigour illustrated in Figures 7a and 7b wherein a higher POMS score indicates a better mood state.

The demographic data and baseline characteristics for the studies 12014A, 12023A and 12013A are provided in tables 3-6 below wherein the medical history according to MedDRA was used for patient selection.

Table 2: Patient Demographics (APRS) – Patients without a sleep disorder at baseline. Studies 12014A, 12023A and 12013A pooled.

		Placebo	Nalmefene	Total
Number of Patients		778	1107	1885
Age	N	778	1107	1885
	Mean	47.01	46.05	46.44
	SD	10.96	11.13	11.07
	Min	28.00	19.00	18.00
	Max	75.00	77.00	77.00

	Median	47.00	46.00	47.00
Age Group n	<25	15	23	38
	25-34	99	159	258
	35-44	190	315	505
	45-54	271	355	626
	55-64	169	189	358
	>=65	34	66	100
Sex n	F	220	291	511
	M	558	816	1374
Race n	Asian	0	3	3
	Black	3	4	7
	Caucasian	773	1099	1872
Race n	Other	2	1	3

Table 3: Baseline Characteristics (APRS) – Patients without a sleep disorder at baseline. Studies 12014A, 12023A and 12013A pooled.

		Placebo	Nalmefene	Total
Monthly number of HDDs	N	778	1105	1883
	Mean	17.80	17.15	17.42
	SD	7.12	7.24	7.20
	Min	0.00	0.00	0.00
	Max	28.00	28.00	28.00
	Median	17.00	16.00	16.00
Total Alcohol Consumption	N	778	1105	1883
	Mean	83.00	79.21	80.78
	SD	44.56	43.13	43.75
	Min	17.00	7.00	7.00
	Max	380.00	447.00	447.00
	Median	73.00	68.00	70.00
POMS – TMD	N	776	1107	1883
	Mean	35.78	36.21	36.03
	SD	36.78	35.87	36.20
	Min	-28.00	-25.00	-28.00
	Max	206.00	169.00	260.00
	Median	27.45	27.00	27.15
POMS – Tension-Anxiety	N	775	1107	1882
	Mean	11.29	11.40	11.35

	SD	6.83	6.73	6.77
	Min	0.00	0.00	0.00
	Max	34.88	35.00	35.00
	Median	10.00	10.00	10.00
POMS – Depression Rejection	N	776	1106	1882
	Mean	13.88	14.03	13.97
	SD	12.21	11.96	12.06
	Min	0.00	0.00	0.00
	Max	60.00	58.00	60.00
	Median	10.00	11.00	11.00
POMS – Anger-Hostility	N	776	1107	1883
	Mean	9.66	10.02	9.87
	SD	7.85	8.06	7.97
	Min	0.00	0.00	0.00
	Max	41.00	47.00	47.00
	Median	8.00	8.00	8.00
POMS - Vigour	N	775	1107	1882
	Mean	14.28	14.60	14.47
	SD	5.92	5.81	5.86
	Min	0.00	0.00	0.00
	Max	30.00	30.00	30.00
	Median	14.40	15.00	15.00
POMS - Fatigue	N	775	1107	1882
	Mean	7.80	7.83	7.82
	SD	5.98	5.89	5.93
	Min	0.00	0.00	0.00
	Max	28.00	27.00	28.00
	Median	7.00	7.00	7.00
POMS - Confusion	N	776	1107	1883
	Mean	7.31	7.53	7.44
	SD	4.69	4.53	4.59
	Min	0.00	0.00	0.00
	Max	26.00	26.00	26.00
	Median	7.00	7.00	7.00

Table 4: Patient Demographics (APRS) – Patients with a sleep disorder at baseline. Studies 12014A, 12023A and 12013A pooled.

	Placebo	Nalmefene	Total

Number of Patients		46	66	112
Age	N	46	66	112
	Mean	49.96	50.15	50.07
	SD	12.31	10.75	11.36
	Min	20.00	23.00	20.00
	Max	70.00	72.00	72.00
	Median	48.50	51.00	50.50
Age Group n	<25	1	1	2
	25-34	6	3	9
	35-44	10	16	26
	45-54	11	22	33
	55-64	10	19	29
	>=65	8	5	13
Sex n	F	19	19	38
	M	27	47	74
Race n	Caucasian	46	66	112

Table 5: Baseline Characteristics (APRS) – Patients with a sleep disorder at baseline. Studies 12014A, 12023A and 12013A pooled.

		Placebo	Nalmefene	Total
Monthly number of HDDs	N	46	66	112
	Mean	18.60	18.29	18.41
	SD	7.53	7.73	7.61
	Min	7.00	6.00	6.00
	Max	28.00	28.00	28.00
	Median	18.50	17.50	18.00
Total Alcohol Consumption	N	46	66	112
	Mean	81.11	94.24	88.85
	SD	52.23	54.24	53.58
	Min	30.00	24.00	24.00
	Max	326.00	296.00	326.00
	Median	66.50	79.00	70.50
POMS – TMD	N	46	65	111
	Mean	52.13	46.79	49.00
	SD	39.89	42.80	41.51
	Min	-9.00	-21.00	-21.00

	Max	142.14	155.00	155.00
	Median	38.00	33.00	38.00
POMS – Tension-Anxiety	N	46	65	111
	Mean	14.35	12.71	13.39
	SD	7.76	7.94	7.87
	Min	0.00	0.00	0.00
	Max	35.00	30.00	35.00
	Median	13.00	11.00	12.00
POMS – Depression Rejection	N	46	65	111
	Mean	19.46	18.40	18.84
	SD	13.28	14.38	13.88
	Min	0.00	0.00	0.00
	Max	53.57	55.00	55.00
	Median	15.00	14.00	14.00
POMS – Anger-Hostility	N	46	65	111
	Mean	12.16	11.16	11.57
	SD	9.05	8.46	8.68
	Min	0.00	0.00	0.00
	Max	33.82	31.00	33.82
	Median	10.00	9.00	10.00
POMS - Vigour	N	46	65	111
	Mean	12.89	13.31	13.14
	SD	6.28	5.84	6.00
	Min	0.00	2.00	0.00
	Max	24.00	27.00	27.00
	Median	13.50	13.00	13.00
POMS - Fatigue	N	46	65	111
	Mean	10.01	9.38	9.64
	SD	7.10	6.78	6.89
	Min	0.00	0.00	0.00
	Max	28.00	26.00	28.00
	Median	9.00	8.00	9.00
POMS - Confusion	N	46	65	111
	Mean	9.04	8.45	8.70
	SD	4.88	5.05	4.97
	Min	2.00	0.00	0.00
	Max	21.00	20.00	21.00
	Median	8.00	7.00	7.00

Example 3: Clinical efficacy measured by SF-36 Mental Component Summary (FAS, OC).

Another method for measuring a patient's health status is by the SF-36 which is a patient-reported outcome developed as a general measure of perceived health status. The mental component summary score focuses on mental aspects of health related quality of life. Higher scores correspond to better health status or well-being.

Data on the mental component summary score are presented in Table 6 below. The difference between nalmefene and placebo in the change from baseline to Week 12 and Week 24 was more pronounced in patients with sleep disorder at baseline than in the patients without sleep disorder at baseline.

Table 6: *Change from Baseline to Week 12 and Week 24 in SF-36 Mental Component Summary (FAS, OC) by Sleep disorder at baseline – Studies 12014A, 12023A and 12013A pooled.*

Sleep disorder at baseline	Baseline		Change to Week 12		Change to Week 24	
Treatment Group	N	Mean±SE	N	Mean±SE	N	Mean±SE
No						
Placebo	695	40.6 ± 0.46	599	3.70 ± 0.44	508	4.58 ± 0.48
Nalmefene	963	40.5 ± 0.39	818	4.73 ± 0.37	628	5.66 ± 0.43
Yes						
Placebo	41	38.1 ± 1.90	34	-0.36 ± 1.82	25	3.13 ± 1.84
Nalmefene	59	37.2 ± 1.64	51	6.55 ± 1.44	39	7.03 ± 1.90

Non-clinical assessment

Further characterization of nalmefene for the treatment of sleep disorders can be assessed in non-clinical models e.g. as outlined in Example 4. Nalmefene can be assessed in said model, or in any other models for assessment of sleep disorder, both as the sole active substance as well as in combination with a second compound.

Nalmefene can be administered e.g. in the form of nalmefene hydrochloride dissolved in an appropriate amount of saline and dosed to the animals e.g. by subcutaneous administration. A second compound to be combined with nalmefene can be dissolved in an appropriate amount of an appropriate vehicle and dosed to the animals e.g. by subcutaneous administration.

Example 4: Rat sleep profiling using electroencephalogram (EEG) recordings.

Rat sleep can qualitatively and quantitatively be assessed using EEG recording. The procedure that can be applied has been previously described by e.g. Depoortere et al., *J. Pharmacol. Exp. Ther.*, (1986), 237:pp. 649–658; Griebel et al., *J. Pharmacol. Exp. Ther.,* (2001) 298: pp. 753–768; Greibel et al., *Behav. Brain Res.* (2012), 232: pp. 416–420. Rats are habituated to the experimental room and recording apparatus for 4 days and to the recording cable for one day prior to each EEG recording session. On the recording day, rats are connected to an EEG recording system by a flexible cable with a rotating collector, allowing rats to move freely. the cable and recording can begin 1 h later lasting at least 3 consecutive days: control day (D0), drug day (D1), control recovery day (D2).

EEG signals are processed by filtering at 1 and 100 Hz (6 dB/octave), then acquired and digitized at 256 Hz using specific software. Activities in the sensorimotor and visual cortices are recorded over the 6-hr recording period by comparison with the reference electrode placed over the cerebellar cortex. Three sleep/wakefulness states of vigilance are considered: (1) Wakefulness characterized by low voltage EEG signal and fast frequency (theta (θ) rhythm: within the 6–9 Hz range) on both cortical derivations; (2) NREMS characterized by high voltage with slow wave (delta (δ) rhythm: within the 1–4 Hz range) with bursts of sleep spindles (sigma (σ) rhythm: within the 10–15 Hz range) on the sensorimotor derivation; (3) REMS by hypersynchronisation of the θ rhythm (within the 4–9 Hz range) in the visual area.

Analysis of the EEG signal is performed automatically by a computerized system able to discriminate between the various sleep phases as demonstrated e.g. by Griebel et al., *Behav. Brain Res.* (2012), 232: pp. 416–420; before being accurately scored by expertly trained human scorers. The parameters considered for examination can be (1) total wakefulness time, (2) total NREMS time, (3) total REMS time, (4) mean duration of NREMS episodes, (5) mean number of NREMS episodes; (6) latency to REMS, (7) mean duration of REMS episodes, and (8) mean number of REMS episodes over the 6-hr recording sessions.

CLAIMS

1. Nalmefene for use in the treatment of a sleep disorder.

2. Nalmefene for use in the treatment of a patient with alcohol dependence who has a co-morbid sleep disorder.

3. Nalmefene for use in the reduction of alcohol consumption in a patient with alcohol dependence who has a co-morbid sleep disorder.

4. Nalmefene according to claim 1 or 2 for use in the treatment of a sleep disorder in a patient with alcohol dependence who has a co-morbid sleep disorder.

5. Nalmefene for use in the reduction of alcohol consumption according to claim 3 and for use in the treatment of a sleep disorder according to claim 4 in a patient with alcohol dependence who has a co-morbid sleep disorder.

6. Nalmefene according to any of claims 1-5, wherein said sleep disorder or co-morbid sleep disorder is an alcohol induced sleep disorder.

7. Nalmefene according to any of claims 2-5, wherein said alcohol dependence is caused by said sleep disorder.

8. Nalmefene according to any of claims 2-5, wherein said alcohol dependence and said sleep disorder are not causally related to each other.

9. Nalmefene according to any of claims 1-8, wherein said sleep disorder or co-morbid sleep disorder is selected from Primary Insomnia, Primary Hypersomnia, Narcolepsy, Breathing-Related Sleep Disorder, Circadian Rhythm Sleep Disorder, Dyssomnia Not Otherwise Specified, Nightmare Disorder, Sleep Terror Disorder, Sleepwalking Disorder, Parasomnia Not Otherwise Specified.

10. Nalmefene according to any of claims 1-9, wherein said nalmefene is the sole active ingredient used in the treatment of said sleep disorder and/or in the reduction of said alcohol consumption.

11. Nalmefene according to any of claims 1-9, wherein said patient is further treated with a second compound which is a hypnotic agent selected from a benzodiazepine or a benzodiazepine receptor agonist; an anticonvulsant; a sedating tricyclic or tetracyclic antidepressant; a melatonin agonist; a sedating antipsychotic; or an antihistamine.

12. Nalmefene according to any of claims 2-11, wherein said patient has a high drinking risk level.

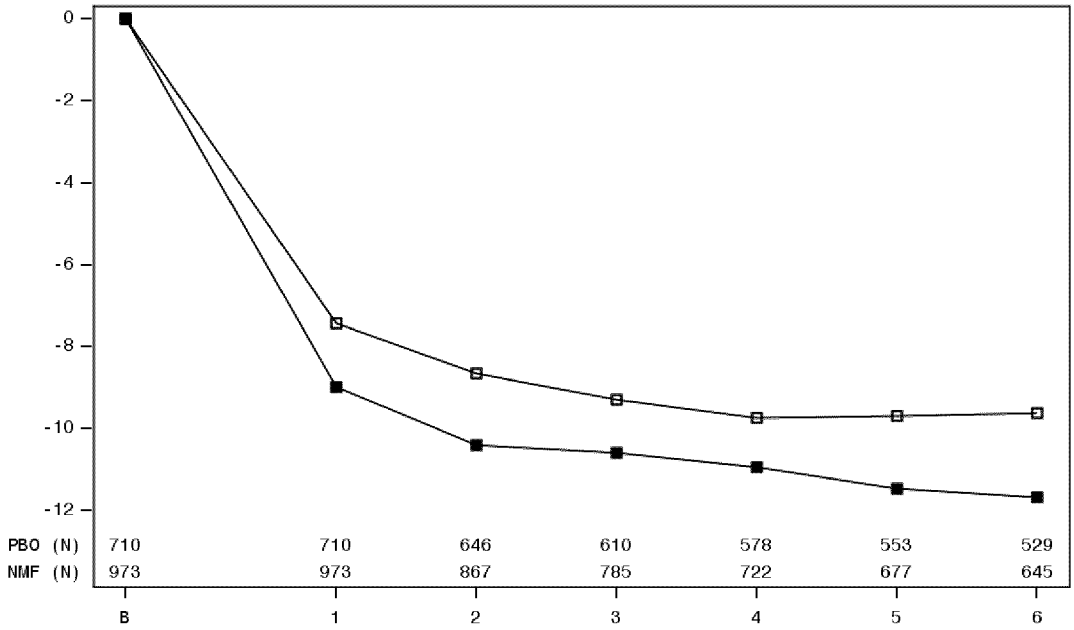
13. Nalmefene according to any of claims 1-12, wherein said nalmefene is used in a dose of 10-20 mg such as 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg or 20 mg.

14. Nalmefene according to any of claims 1-13, wherein said nalmefene is used in the form of a hydrochloride salt.

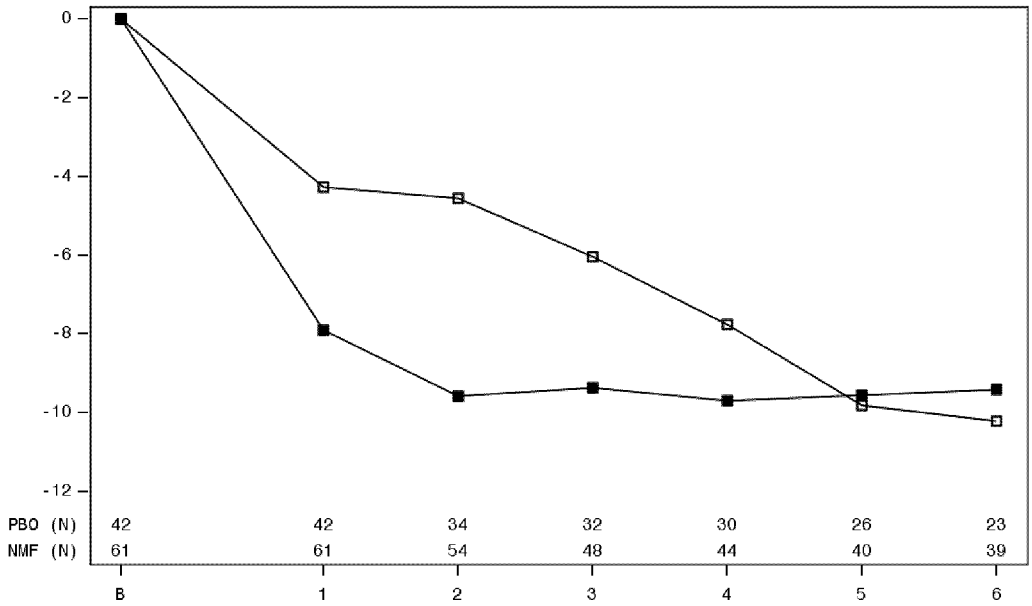
15. Nalmefene according to any of claims 1-14, wherein said nalmefene is contained in an oral dose form such as tablets or capsules.

FIGURES

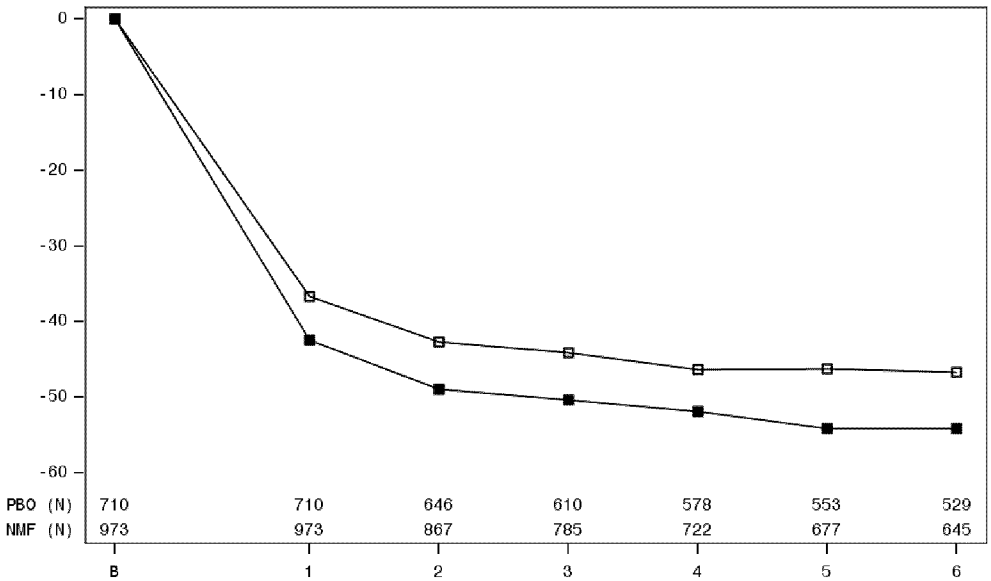
1a



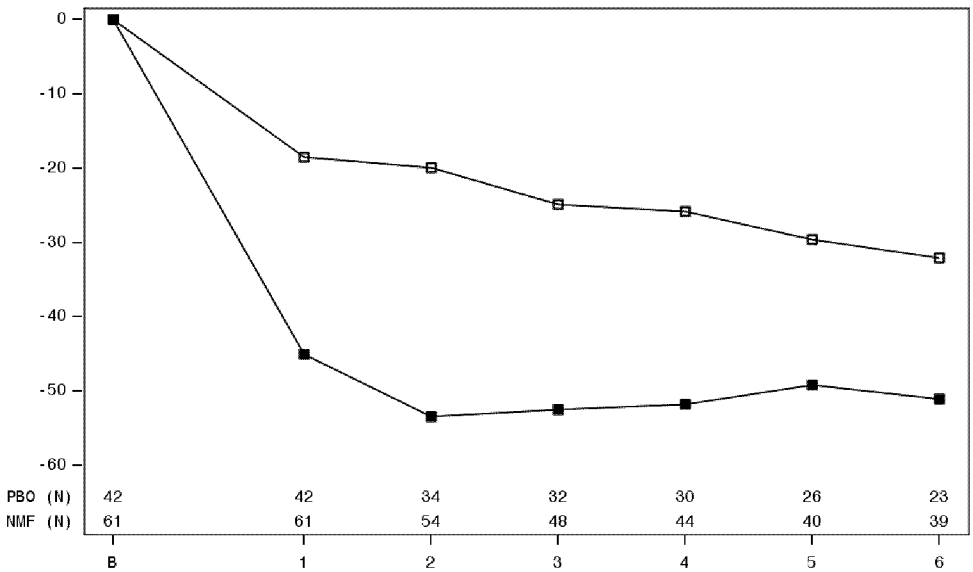
1b



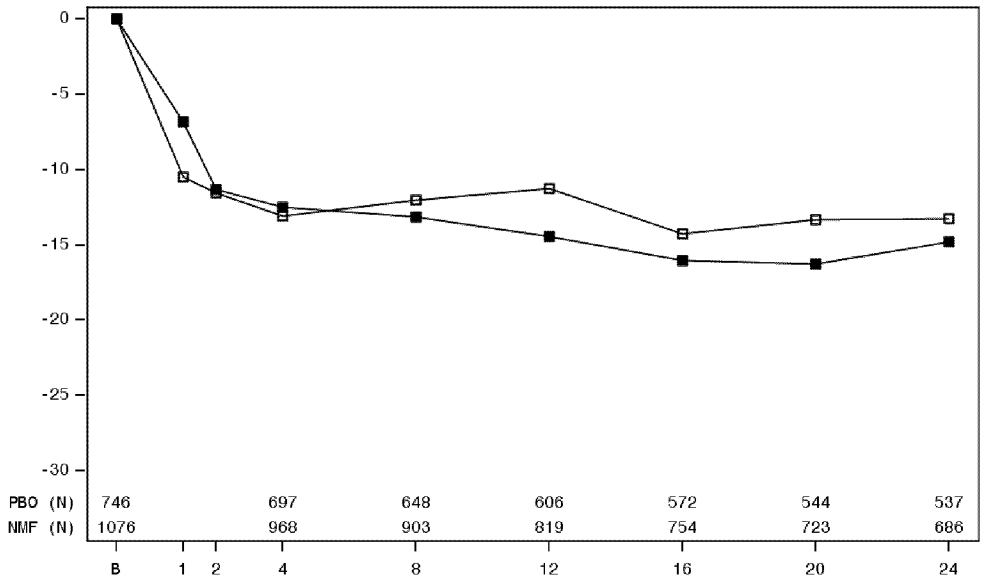
2a


0
-10
-20
-30
-40
-50
-60
PBO (N) 710 710 646 610 578 553 529
NMF (N) 973 973 867 785 722 677 645
B 1 2 3 4 5 6

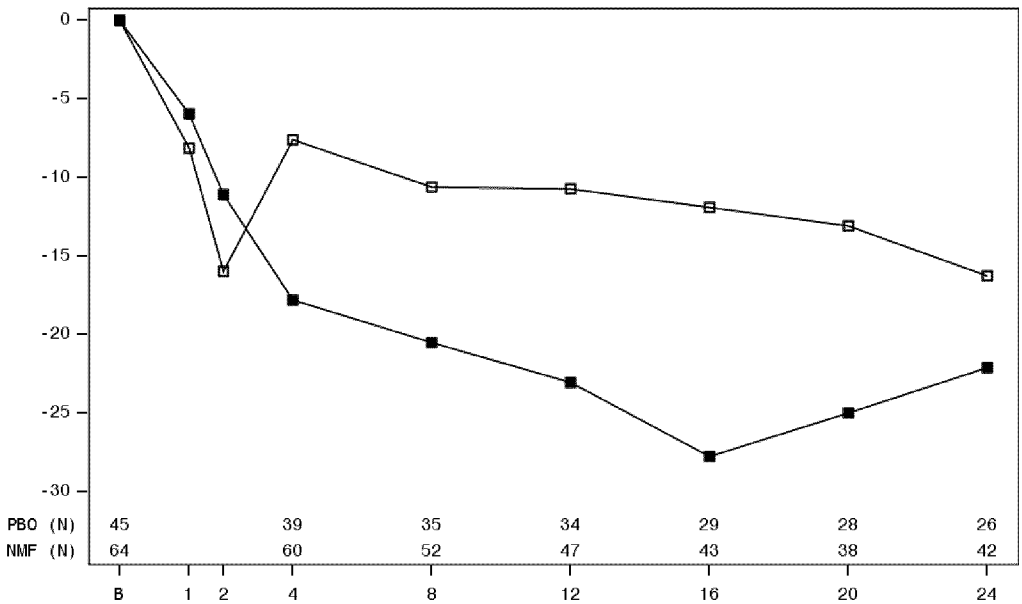
2b


0
-10
-20
-30
-40
-50
-60
PBO (N) 42 42 34 32 30 26 23
NMF (N) 61 61 54 48 44 40 39
B 1 2 3 4 5 6

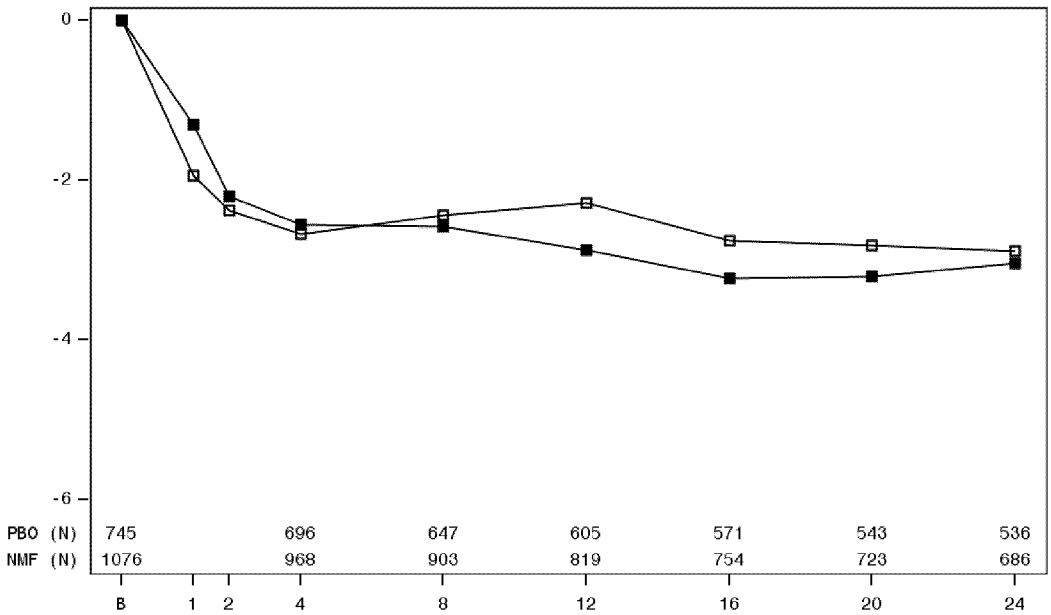
3a


0
-5
-10
-15
-20
-25
-30
PBO (N) 746 697 648 606 572 544 537
NMF (N) 1076 968 903 819 754 723 686
B 1 2 4 8 12 16 20 24

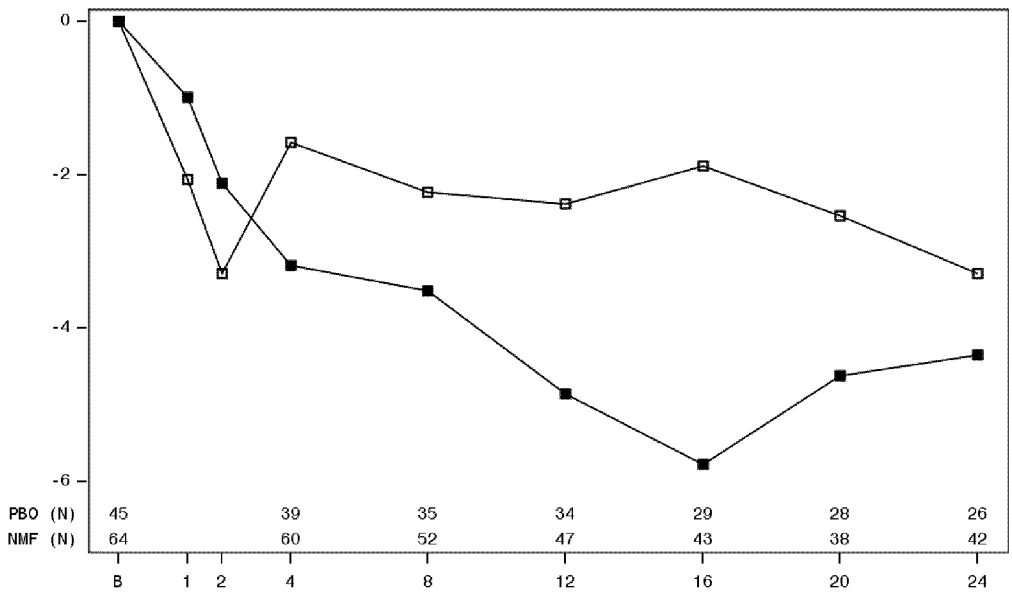
3b


0
-5
-10
-15
-20
-25
-30
PBO (N) 45 39 35 34 29 28 26
NMF (N) 64 60 52 47 43 38 42
B 1 2 4 8 12 16 20 24

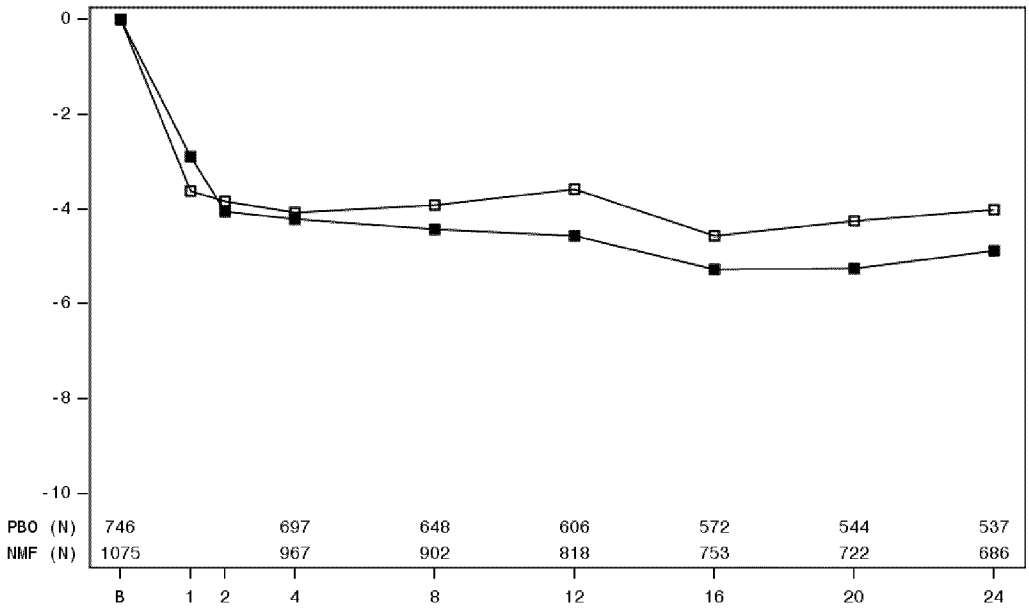
4a


0
-2
-4
-6
PBO (N) 745 696 647 605 571 543 536
NMF (N) 1076 968 903 819 754 723 686
B 1 2 4 8 12 16 20 24

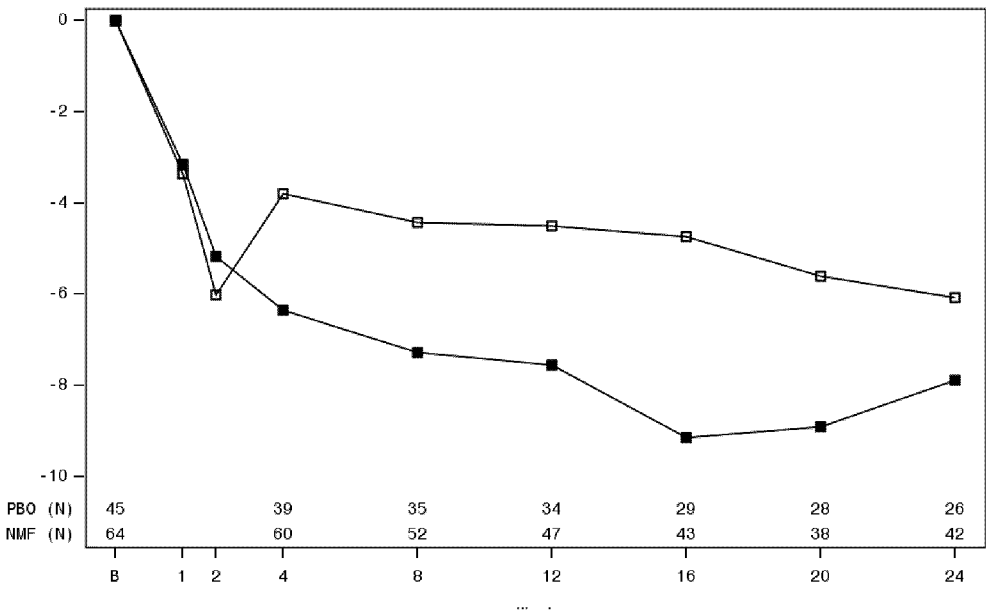
4b


0
-2
-4
-6
PBO (N) 45 39 35 34 29 28 26
NMF (N) 64 60 52 47 43 38 42
B 1 2 4 8 12 16 20 24

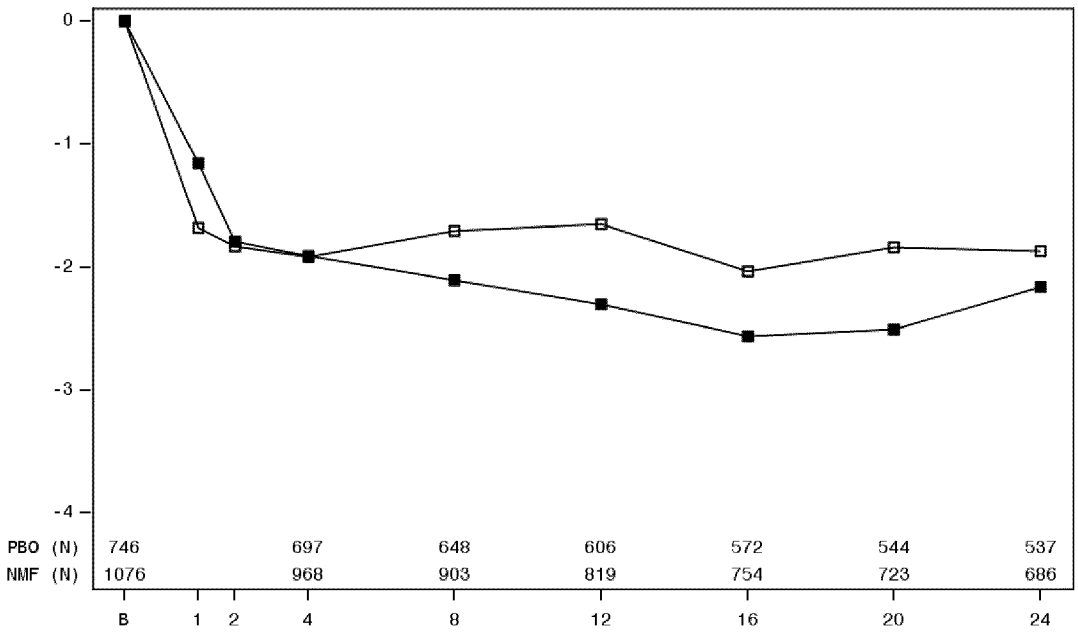
5a


0
-2
-4
-6
-8
-10
PBO (N) 746 697 648 606 572 544 537
NMF (N) 1075 967 902 818 753 722 686
B 1 2 4 8 12 16 20 24

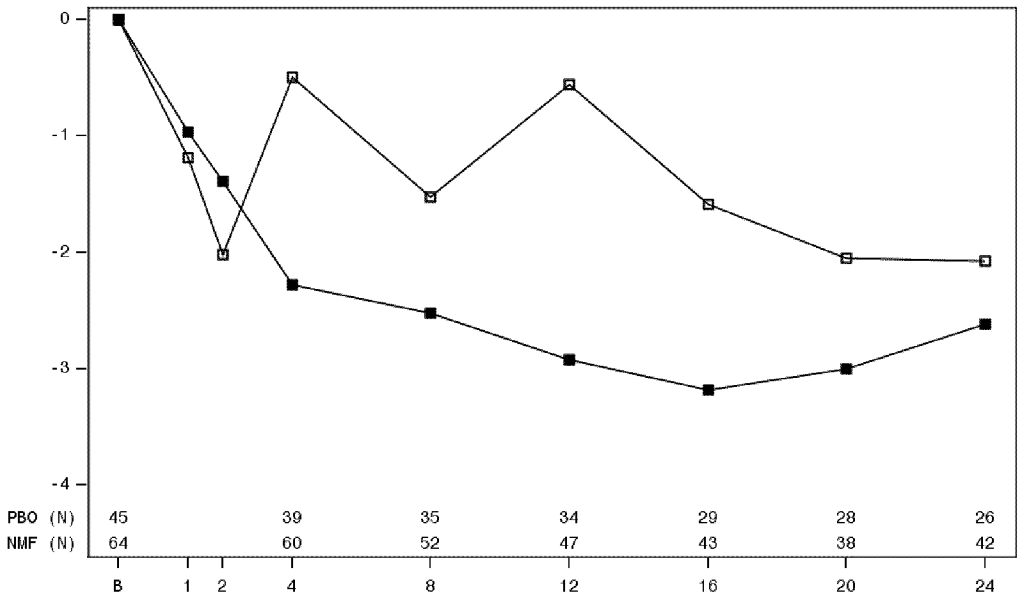
5b


0
-2
-4
-6
-8
-10
PBO (N) 45 39 35 34 29 28 26
NMF (N) 64 60 52 47 43 38 42
B 1 2 4 8 12 16 20 24

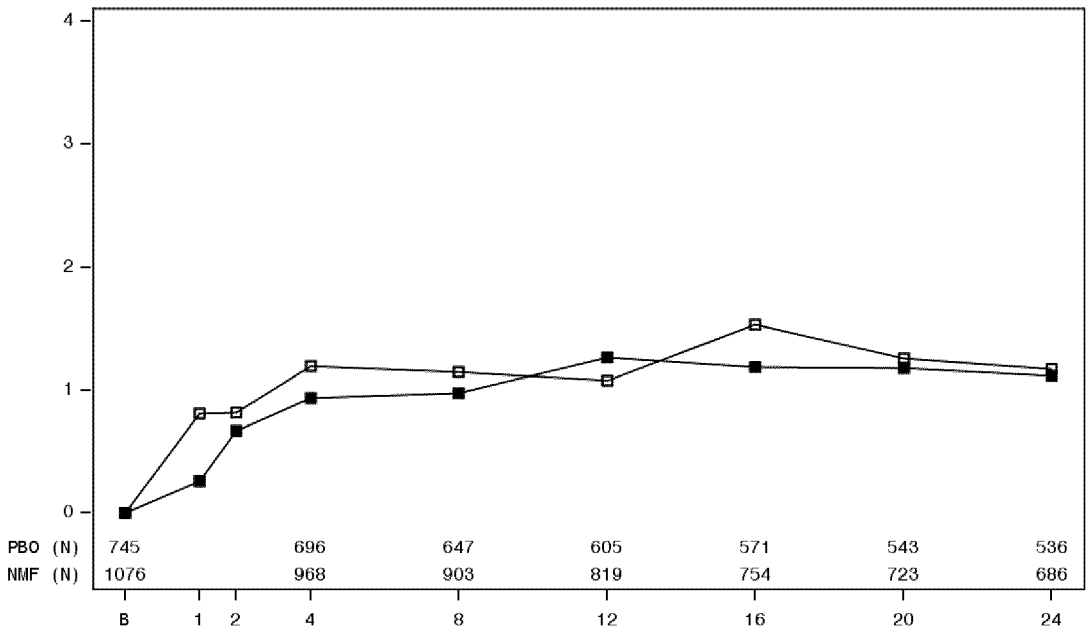
6a


0
-1
-2
-3
-4
PBO (N) 746 697 648 606 572 544 537
NMF (N) 1076 968 903 819 754 723 686
B 1 2 4 8 12 16 20 24

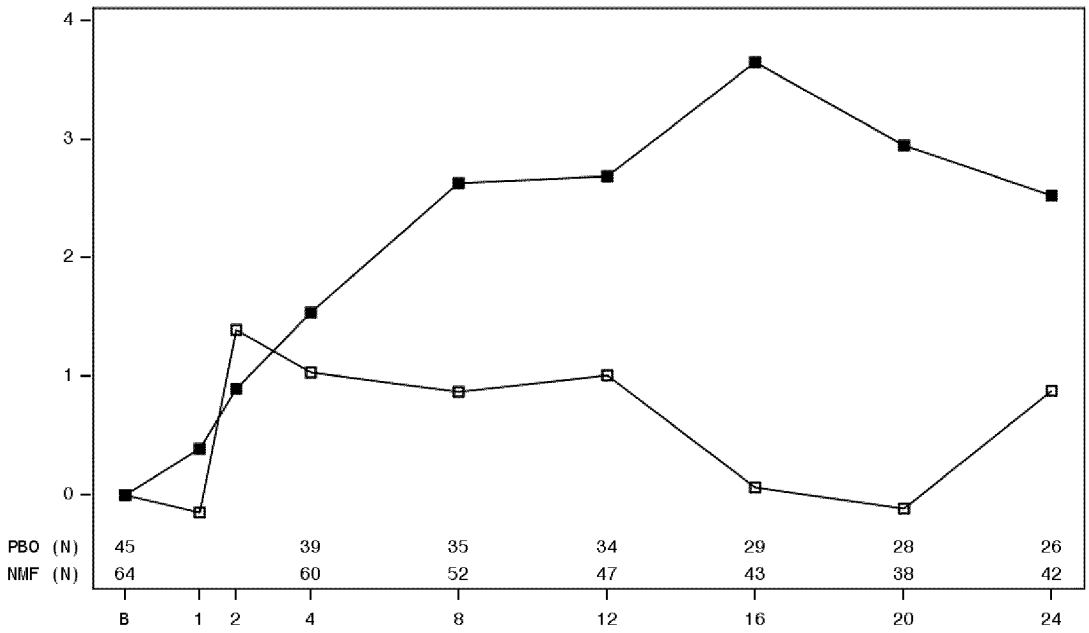
6b


0
-1
-2
-3
-4
PBO (N) 45 39 35 34 29 28 26
NMF (N) 64 60 52 47 43 38 42
B 1 2 4 8 12 16 20 24

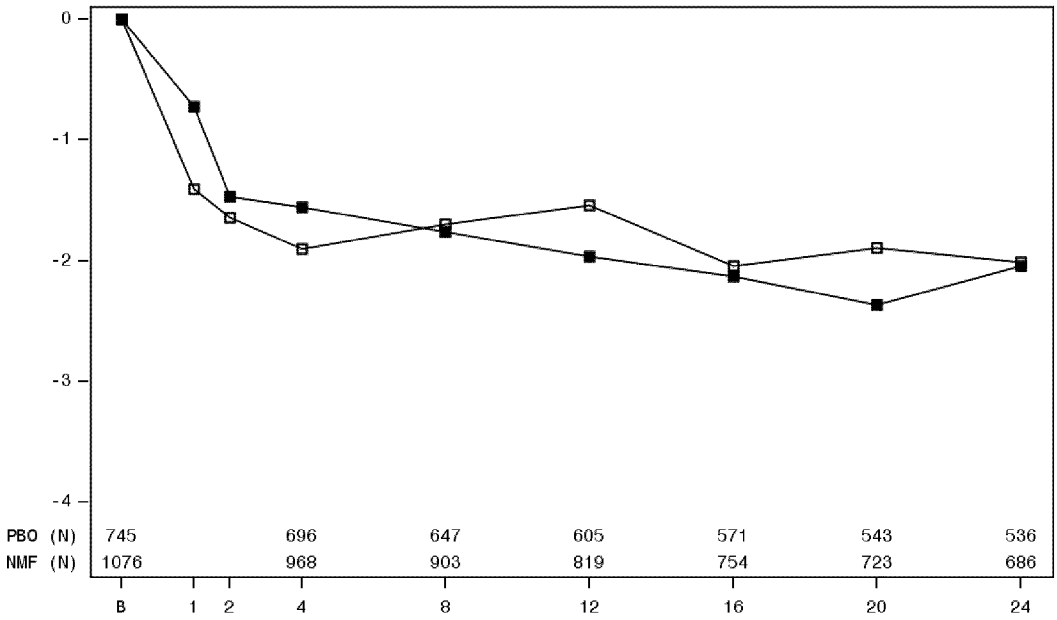
7a


4
3
2
1
0
PBO (N) 745 696 647 605 571 543 536
NMF (N) 1076 968 903 819 754 723 686
B 1 2 4 8 12 16 20 24

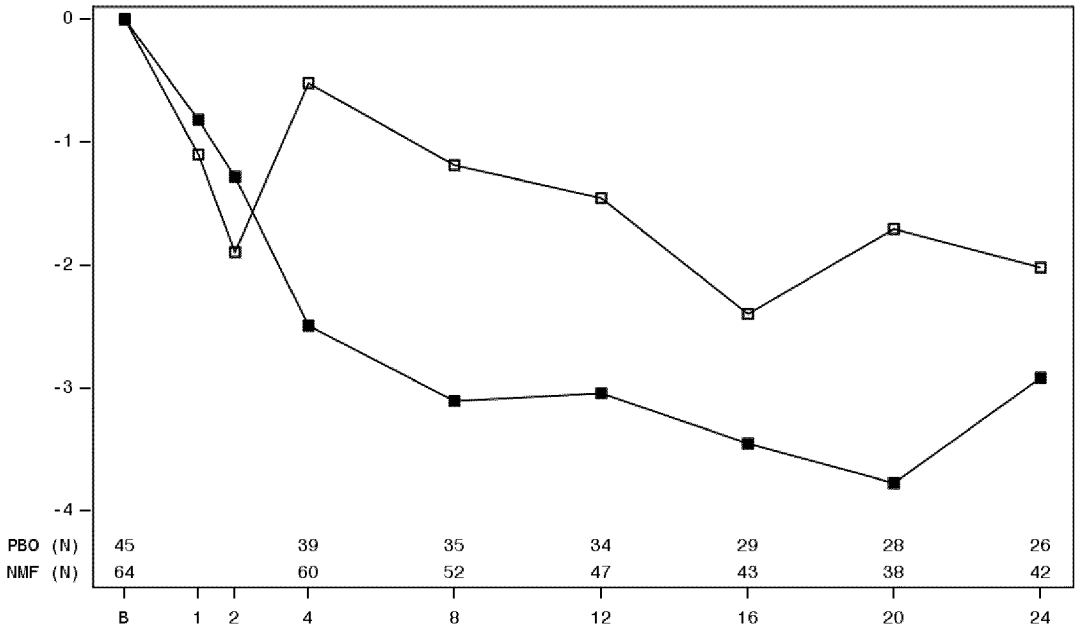
7b


4
3
2
1
0
PBO (N) 45 39 35 34 29 28 26
NMF (N) 64 60 52 47 43 38 42
B 1 2 4 8 12 16 20 24

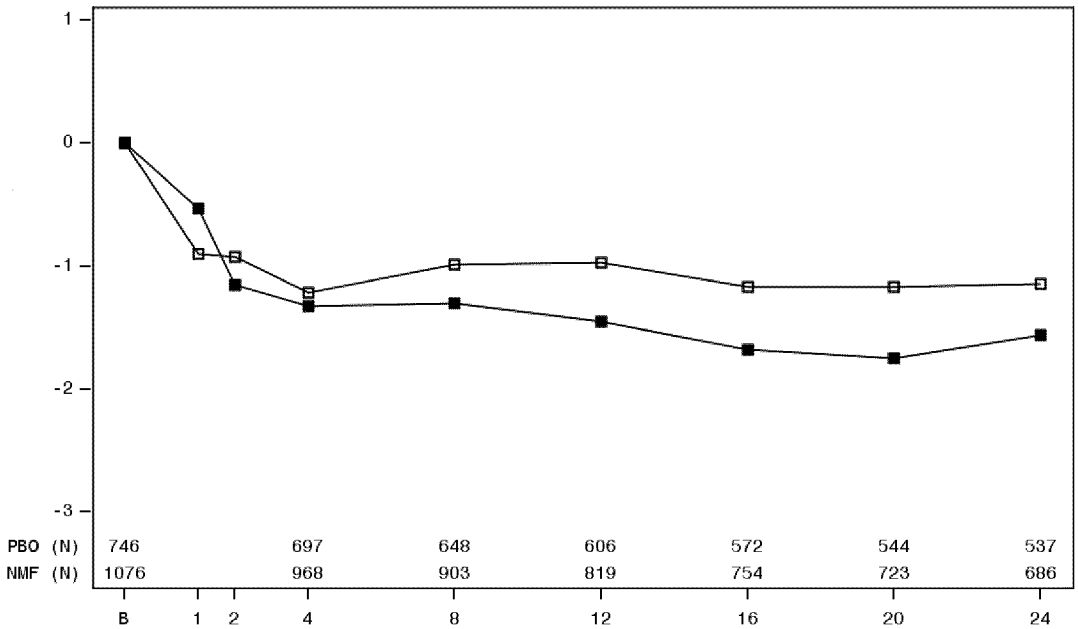
8a


0
-1
-2
-3
-4
PBO (N) 745 696 647 605 571 543 536
NMF (N) 1076 968 903 819 754 723 686
B 1 2 4 8 12 16 20 24

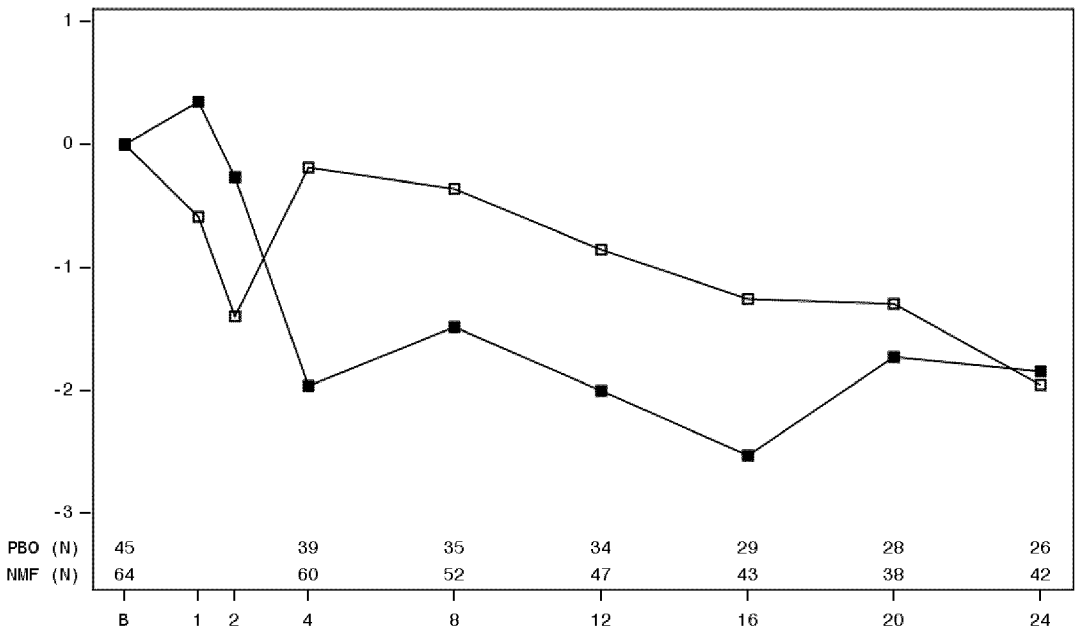
8b


0
-1
-2
-3
-4
PBO (N) 45 39 35 34 29 28 26
NMF (N) 64 60 52 47 43 38 42
B 1 2 4 8 12 16 20 24

9a


1
0
-1
-2
-3
PBO (N) 746 697 648 606 572 544 537
NMF (N) 1076 968 903 819 754 723 686
B 1 2 4 8 12 16 20 24

9b


1
0
-1
-2
-3
PBO (N) 45 39 35 34 29 28 26
NMF (N) 64 60 52 47 43 38 42
B 1 2 4 8 12 16 20 24

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/057681

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/485 A61P25/20 A61P25/32
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 451 009 A2 (HILLEL GLOVER [US]) 9 October 1991 (1991-10-09) example 1	1,9-11, 13,15

Y	WO 91/18605 A1 (SINCLAIR JOHN D [FI]; SCHEININ HARRY [FI]; LAMMINTAUSTA RISTO [FI]) 12 December 1991 (1991-12-12) page 9, line 29 - page 10, line 5	2-15

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 June 2014	17/06/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Allnutt, Sarah

3

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/057681

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ROSA M. CRUM ET AL: "Association of Sleep Disturbance with Chronicity and Remission of Alcohol Dependence: Data from a Population-Based Prospective Study", ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH., vol. 28, no. 10, 1 October 2004 (2004-10-01), pages 1533-1540, XP055121597, US ISSN: 0145-6008, DOI: 10.1097/01.ALC.0000141915.56236.40 abstract -----	2-15
X,P	WO 2014/001427 A1 (LUNDBECK & CO AS H [DK]) 3 January 2014 (2014-01-03) page 33 - page 39 -----	2-15

3

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/057681

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0451009	A2	09-10-1991	AU	644145	B2	02-12-1993
			AU	7373591	A	03-10-1991
			CA	2038539	A1	23-09-1991
			EP	0451009	A2	09-10-1991
			IL	97463	A	24-01-1995
			JP	H05105629	A	27-04-1993
			US	5028612	A	02-07-1991
WO 9118605	A1	12-12-1991	AT	145329	T	15-12-1996
			AU	642748	B2	28-10-1993
			CA	2084519	A1	05-12-1991
			DE	69123247	D1	02-01-1997
			DE	69123247	T2	15-01-1998
			DK	0531415	T3	09-12-1996
			EP	0531415	A1	17-03-1993
			ES	2097209	T3	01-04-1997
			FI	925513	A	04-12-1992
			GR	3022289	T3	30-04-1997
			HU	210637	B	28-06-1995
			IE	911888	A1	04-12-1991
			JP	3059213	B2	04-07-2000
			JP	H06506665	A	28-07-1994
			LT	1486	A	25-09-1995
			LV	10190	A	20-10-1994
			NZ	238391	A	24-06-1997
			RU	2090190	C1	20-09-1997
			US	5086058	A	04-02-1992
			WO	9118605	A1	12-12-1991
			ZA	9104185	A	29-07-1992
WO 2014001427	A1	03-01-2014	US	2014005216	A1	02-01-2014
			US	2014005217	A1	02-01-2014
			WO	2014001427	A1	03-01-2014