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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Selincro

International non-proprietary name: NALMEFENE

Procedure No. EMEA/H/C/002583/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

%CDT	percent carbohydrate-deficient transferrin
AD	Alcohol dependence
ADS	Alcohol Dependence Scale
AE	Adverse event
AI	Accumulation index
ALAT	Alanine aminotransferase
AP	Action potential
APRS	All patients randomised set
APTS	All patients treated set
AUC	Area under the concentration vs. time curve
BAC	Blood alcohol concentration
BOCF	Baseline observation carried forward
CD50	Dose causing convulsions in 50% of animals
CGI-I	Clinical Global Impression- Global improvement
CGI-S	Clinical Global Impression – Severity of illness
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CIWA-Ar	Clinical Institute Withdrawal Assessment for Alcohol scale
C _{max}	Maximum plasma concentration
CNS	Central nervous system
DADLE	D-ala-D-leu-enkephalin
DAMGO	Tyr-D-Ala-Gly-NMe-Phe-Gly-ol
DrInC-2R	Drinker Inventory of consequences
DRL	Drinking risk level
DSM-IV-2R	Diagnostic and Statistical Manual of Mental Disorders, 4th Edit. Text Revision
ECG	Electrocardiogram
FAS	Full analysis set
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
HDD	Heavy drinking day
HEK 293	Human embryonic kidney cell line
HERG	Human ether-a-go-go-related gene (HERG-1 is the potassium channel encoded by this gene)
IC50	Concentration causing 50% inhibition
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IP	Intraperitoneal injection
IP3	Inositol triphosphate
IR	Immediate release
it	Intrathecal
ITMB	Intended to be marketed
iv	Intravenous
K _d	Equilibrium dissociation constant
K _i	Inhibition constant
LOCF	Last observation carried forward
MAA	Marketing Authorisation Application
MCV	Mean corpuscular volume
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed model repeated measures
MTP	Main treatment period
NMF	Nalmefene
NC	Not calculable
NDD	Non-drinking day
NMF	Nalmefene HCl
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NS	No sample available
OC	Observed cases

PBO	Placebo
PD	Pharmacodynamics
PK	Pharmacokinetics
PMI	Placebo mean imputation
po	oral
RLDRL	Response defined as a downward shift from baseline in DRL to low DRL or below
ROP	Run-out period
RSDRL	Response defined as a downward shift from baseline in DRL; for patients with a very high DRL at baseline: a shift to medium DRL or below, and for patients with a high or medium DRL at baseline: a shift to low DRL
SAE	Serious adverse events
sc	Subcutaneous
SE	Standard error
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
TAC	Total alcohol consumption
TEAE	Treatment-emergent adverse events
TLFB	Timeline followback
Tmax	Time to maximum plasma concentration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant H. Lundbeck A/S submitted on 25 November 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Selincro, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2011. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication: "reduction of alcohol consumption in patients with alcohol dependence".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/293/2010 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

New active Substance status

The applicant requested the active substance nalmefene contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 30 May 2008 (EMEA/H/SA/185/2/2008/II). The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

No marketing authorisation for nalmefene was issued in the EU at the time of submission of the Marketing Authorisation Application for Selincro. While parenteral formulations of nalmefene are registered in the US and Canada, none are available on those markets at the time of submission of this Marketing Authorisation Application. Parenteral formulations are also available and are marketed for *“the treatment and management of known or suspected opioid overdose and to reverse the effects induced by total or partial natural or synthetic opioids, including respiratory depression”* and for the either the *“complete or partial reversal of opioid effects, including natural or synthetic opioid-induced respiratory depression”* or for *“known or suspected opioid overdose or poisoning, first aid awaking, acute brain and spinal cord injury, cerebral ischaemia, cerebral infarction and other neurological dysfunction disease, coma, shock, postoperative wake-up anaesthesia, alcoholism, and drug treatment relapse after release”* in Mexico and China, respectively.

1.2. Manufacturers

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Denmark

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2881, Route des Crêtes
BP 205
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France

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Martina Weise

Co-Rapporteur: Patrick Salmon

- The application was received by the EMA on 25 November 2011.
- The procedure started on 21 December 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2012.
- During the meeting on 19 April 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 April 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 July 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 03 September 2012.
- During the CHMP meeting on 20 September 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 October 2012.
- During a meeting of the BS Working Party in October 2012, experts were convened to address questions raised by the CHMP.
- During a meeting of a SAG psychiatry on 6 November 2012, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 14 November 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 15 November 2012, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 21 November 2012.
- During the meeting on 13 December 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Selincro on 13 December 2012.

2. Scientific discussion

2.1. Introduction

This application is a centralised Marketing Authorisation Application (MAA) made by H. Lundbeck A/S for Selincro 18 mg film-coated tablets (as 21.917 mg nalmefene hydrochloride dihydrate, corresponding to 20 mg nalmefene hydrochloride and 18.06 nalmefene as base) to be taken as-needed for the reduction of alcohol consumption in patients with alcohol dependence (AD).

Acute alcohol intake results in mesolimbic dopamine release (facilitated by the release of β -endorphins), which can provide positive reinforcement. However, after repeated exposure to high doses of alcohol, neuroadaptations occur in several neurotransmitter/ neuropeptide systems, including the opioid receptor system, which drives continued alcohol intake.

Nalmefene is an opioid system modulator with a distinct μ , δ , and κ receptor profile. *In vitro* studies show 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. *In vivo* studies have demonstrated that nalmefene reduces alcohol consumption, possibly by modulating cortico-mesolimbic functions, thus reducing the reinforcing effects of alcohol.

On 30 May 2008, Lundbeck obtained EMA Scientific Advice on the clinical development programme for nalmefene and the design of the clinical studies that constitute the pivotal studies of this MAA.

On 18 February 2010, the Committee for Medicinal Products for Human Use (CHMP) adopted the EMA Guideline on alcohol dependence, which came into effect 1 September 2010. According to this guideline, the goals of alcohol dependence treatment include the achievement of abstinence, reduction in frequency and severity of relapse, and improvement in health and psychosocial functioning. The main focus of this guideline is therefore on products that are developed as an aid to achieve and maintain abstinence as the ultimate treatment goal in patients with alcohol dependence. This includes products to prevent relapses after initiated abstinence, as well as products leading to clinically significantly reduced alcohol consumption as an intermediate goal (harm reduction approach) on the way to full abstinence.

For the intermediate harm reduction goal (significant moderation without prior detoxification) efficacy should be expressed by change to baseline in total consumption of alcohol (TAC, per month, presented as amount of pure alcohol in grams per day) as well as by reduction in number of Heavy Drinking Days (HDD defined as more than 60 grams of pure alcohol in men and 40 grams in women). Both are considered primary variables.

Reduction of alcohol consumption as a clinical significant treatment goal is widely accepted in current literature reports (*White Paper*, jointly released by Wim van den Brink, University of Amsterdam, NL, Antoni Gual, Hospital Clinic Barcelona, ES and Karl Mann, University of Heidelberg, DE).

Medicines that are currently approved in many countries for relapse prevention in alcohol dependence are disulfiram, acamprosate and naltrexone. All three are only recommended as adjunctive to psychosocial counselling in motivated patients. In the pivotal trials supporting this MAA, nalmefene was also administered in conjunction with regular psychological motivation-enhancing interventions.

The concept of applying opioid receptor antagonists to interfere with the mesolimbic rewarding system, counteracting the positive reinforcement effects in alcohol dependence is not new and has been widely described in literature reviews. Another competitive μ -opioid receptor antagonist, naltrexone, was already licensed in several European countries as a pharmacological treatment approach, adjunct to an encompassing psychosocial treatment concept, in an effort to maintain abstinence and to prevent relapse.

The applicant applied for the following indication: "reduction of alcohol consumption in patients with alcohol dependence".

The final indication recommended by the CHMP as most accurately reflecting the pivotal trial data and specifying the most appropriate target population and prescribing conditions for nalmefene treatment, was as follows:

Selincro is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (see section 5.1), without physical withdrawal symptoms and who do not require immediate detoxification.

Selincro should only be prescribed in conjunction with continuous psychosocial support focussed on treatment adherence and reducing alcohol consumption.

Selincro should be initiated only in patients who continue to have a high drinking risk level two weeks after initial assessment.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as oval biconvex white film-coated tablets engraved with "S", available in only one strength, containing 21.917 mg nalmefene hydrochloride dihydrate (corresponding to 20 mg nalmefene hydrochloride, 18.06 nalmefene as base), as active substance. The full composition is described in section 6.1 of the SmPC.

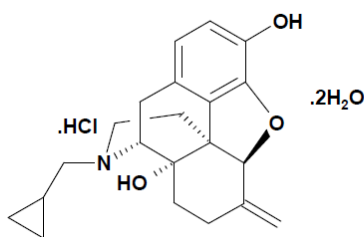
The product is available in PVC/PVDC/alu blisters inside an outer carton box.

2.2.2. Active Substance

Nalmefene hydrochloride dihydrate is a white or almost white crystalline powder.

The chemical name is 17-(Cyclopropylmethyl)-4,5- α -epoxy-6-methylene-morphinan-3,14-diol hydrochloride dihydrate, has the following molecular formula $C_{21}H_{25}NO_3 \cdot HCl \cdot 2 H_2O$ and structure:

Structural Formula:



Nalmefene hydrochloride dihydrate is very soluble in water and is not hygroscopic.

Nalmefene hydrochloride dihydrate is a chiral compound, containing 4 asymmetric carbon atoms.

Only one crystal form of Nalmefene hydrochloride dihydrate has been identified. Nalmefene hydrochloride dihydrate does not melt, but becomes amorphous after dehydration.

The structure of nalmefene hydrochloride dihydrate was demonstrated by elemental analysis, IR, UV/Vis, ¹H-NMR and ¹³C-NMR spectroscopy as well as MS spectrometry. Its crystal structure was analysed by X-ray diffraction and specific optical rotation was determined. It has been shown that no polymorphic forms were observed.

Manufacture

The active substance is sourced from two active substance manufacturers.

Nalmefene hydrochloride dihydrate is manufactured synthetically.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided and it was considered satisfactory.

Specification

The active substance specification includes tests for identification (FT-IR, HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), water content (KF), heavy metals, and particle size.

Batch analysis data were provided for several batches, including commercial scale batches, produced with the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly.

All compendial and in-house test methods are adequately validated.

Stability

The active substance is packaged in PE bags as primary and in HDPE drums as secondary packing material.

Batches of active substance (commercial scale, included) packed in the intended commercial package from the proposed manufacturer were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up to 36 months, and accelerated (40°C/75%RH) for up to 6 months. Satisfactory results on stress conditions (e.g. photostability, acid, hydrolysis and oxidation) were also provided.

The following parameters were tested: description, identification, water content, related substances and assay.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 3 years in the proposed container closure system in order to protect from light.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The development of the formulation has been well described and the manufacturing process justified. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

There are no overages used in the manufacturing process.

The discriminatory power of the dissolution method has been demonstrated.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

A standard manufacturing process is used to manufacture the film-coated immediate release tablets.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and has been demonstrated to be capable and to be able to reproducibly produce finished product of the intended quality. The in process controls are adequate for this pharmaceutical form.

The batch analysis data on pilot scale and production scale batches shows that the medicinal product can be manufactured reproducibly according to the agreed finished product specification.

Product specification

The finished product release specifications include appropriate tests for description, identification (HPLC and UV), assay (HPLC), uniformity of dosage units, dissolution, water content (KF), degradation products (HPLC) and microbial quality.

All analytical procedures and test methods have been adequately described and the validation data presented is acceptable.

Batch data including production scale batches confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data of batches stored in a container closure system equivalent to that proposed for marketing were provided under long term conditions for up to 18 months (25 °C/60 % RH) and for up to 6 months under accelerate conditions (40 °C/75 % RH), in line with ICH guidelines.

Samples were tested for description, related substances, assay, dissolution and water content.

Photostability studies were conducted and indicate that drug product is not sensitive to light.

All investigated parameters remain within specified limits. The stability studies provided support the shelf-life under the storage conditions declared in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

In support of their MAA, Lundbeck submitted a complete non-clinical pharmacology, pharmacokinetic and toxicology programme for nalmefene. Pharmacological as well as toxicological properties of the drug were comprehensively investigated and published in scientific journals. The data submitted were assessed on the legal basis of the application, applicable guidelines and other scientific criteria.

2.3.2. Pharmacology

Nalmefene was tested in a full and comprehensive non-clinical strategy comprising appropriate studies on pharmacology, safety pharmacology and pharmacodynamics drug interactions. The testing strategy followed the package of guidelines of both ICH and CHMP. Safety pharmacology studies were in compliance with the GLP requirements.

Primary Pharmacology

Nalmefene was tested in a full and comprehensive non-clinical strategy comprising appropriate studies on pharmacology, safety pharmacology and pharmacodynamics drug interactions. The testing strategy followed the package of guidelines of both ICH and CHMP. Safety pharmacology studies were in compliance with the GLP requirements with the exception of one study (Cardiovascular action of an intravenous dose of nalmefene in dogs). However, since the results of this study confirm the results obtained in another GLP-compliant study in the same specie (BTT31-PD025), the results obtained were considered adequate.

Comprehensive *in vitro* studies were performed to characterize the mode of action of nalmefene. It has been shown that nalmefene is a selective opioid receptor ligand without any significant affinity to targets apart from opioid receptors. On the opioid receptor subtypes nalmefene has equal high affinity

for μ , and κ opioid receptors respectively, and medium affinity for δ opioid receptors. The binding affinity of nalmefene at opioid receptor subtypes is summarized in the table below:

Opioid receptor	Assay	K _i (nM)
δ	δ opioid receptor, human, agonist ligand [³ H] DADLE	16
	δ opioid receptor, human, antagonist ligand [³ H] naltrindole	53
κ	κ opioid receptor, rat, agonist ligand [³ H] U-69593	0.31
	κ opioid receptor, human, antagonist ligand [³ H] diprenorphine	1.1
	κ opioid receptor, human, antagonist ligand [³ H] diprenorphine	0.64
μ	μ opioid receptor, human, agonist ligand [³ H] DAMGO	0.20
	μ opioid receptor, human, antagonist ligand [³ H] diprenorphine	1.3

With respect of functional activity, the drug behaves as moderately potent δ opioid antagonist and as a potent κ opioid partial agonist. The functional activity of nalmefene at μ opioid receptors *in vitro* is dependent on the biological test system. In contrast to the *in vitro* studies nalmefene acts clearly as a μ opioid antagonist without any agonistic activity under *in vivo* conditions. This has been shown in established animal models reflecting μ receptor specificity (tail-flick test, writhing test, tail skin temperature, morphine antagonism in rhesus monkeys).

The main metabolite of nalmefene in rats is nornalmefene, which showed some agonist activity in guinea pig membrane and in the rat tail flick and hot plate test (intrathecal administration), but was without any agonistic activity after systemic administration. Nalmefene-3-O-glucuronide, a major metabolite in dog and man, was inactive at μ opioid receptors. Thus, the activity of nornalmefene-3-O-glucuronide at the opioid receptors is unlikely to contribute to the pharmacological effect of nalmefene in humans. Nalmefene 3-O sulphate, a minor human metabolite displayed the same receptor profile as well as functional activity as the parent drug.

As shown in three models of alcohol-dependent rats, nalmefene significantly reduced voluntary alcohol consumption. The effect was still present 24 hours after the last injection, which can be explained by the slow dissociation rate of nalmefene from the μ opioid receptor. Under the conditions of repeated administration, the effect remained stable. With respect of the potential clinical usage of nalmefene, it should be noted that nalmefene prevented an alcohol deprivation effect, i.e. an increase in alcohol consumption after a prolonged period of alcohol abstinence. Therefore, the non-clinical data support the clinical use of nalmefene.

Secondary Pharmacology

No specific secondary pharmacology studies were performed. The potential dependence liability of nalmefene was assessed in rhesus monkeys (see other toxicity studies, section 2.3.4).

Safety pharmacology programme

Cardiovascular system

The effect of nalmefene on the cardiovascular system has been extensively studied. Both under *in vitro* and *in vivo* conditions defined effects have been observed. Dose-dependent inhibition of HERG-1 tail current without any other abnormal features such as pre and after depolarization were found, but this effect occurred at concentration approximately 12-fold to 300-fold the clinically relevant range. In

Purkinje fibres a moderate decrease of APD was observed. A thorough study in telemetered dogs revealed consistently a significant prolongation of the QRS duration after an oral dose of 25 or 50 mg/kg. Taking into consideration that the doses used were far above pharmacodynamic relevant range and the small effect even after 50 mg/kg, it is concluded that this effect is without clinical relevance.

Respiratory system

Nalmefene had no significant effects on the respiration rate or tidal volume of rats when administered at 50, 100 and 150 mg/kg. At the highest dose the corresponding plasma concentration (C_{max}) of nalmefene was in the range from 754 to 3406 ng/ml.

Central nervous system

In the IRWIN test for central effects no significant gross behavioural or physiological changes were observed in rats orally administered 50 mg/kg. Higher doses produced consistent effects on neurological behaviour (passivity, increased touch response, increased grip strength, urination). Other behavioural endpoints were evaluated in the studies performed to assess dependence (see other toxicity studies, section 2.3.4).

In summary, the pharmacology data demonstrate that nalmefene is an opioid system modulator with a distinct profile on μ , κ , and δ opioid receptors without any significant affinity to targets apart from opioid receptors. With respect to the scientific rationale, it has been shown in accepted animal models of alcohol dependence, that nalmefene effectively suppresses voluntary alcohol intake even after repeated administration. The results of the safety pharmacology studies do not raise concerns.

The CHMP noted the lack of a κ opioid receptor occupancy study. The applicant acknowledged the possible involvement of κ receptor activity as part of nalmefene's mode of action, and explained that an appropriate receptor study was underway. Their strategy is to exactly reproduce the experimental conditions described by Need *et al* (2007). The Applicant was requested to submit the κ opioid receptor occupancy data for review when completed.

Pharmacodynamic Drug interactions

The potential interaction of nalmefene with the benzodiazepine antagonist flumazenil was investigated using i.v. route in rats with an administration ratio of flumazenil/nalmefene of 23:1, since from earlier studies it was known that both drugs have the potential to elicit clonic seizures. Whereas for flumazenil and nalmefene the CD50 (dose that elicits clonic seizures in 50% of the animals) values were 167.8 and 7.45 mg/kg respectively, the mixture of both drugs yielded a CD50 value of 106.3 mg/kg, thus pointing to sub-additive interaction. This is not likely to have clinical implications since the doses used were far higher than those used under clinical conditions.

2.3.3. Pharmacokinetics

The pharmacokinetics of nalmefene and/or its metabolites were evaluated in mice, male and female rats, dogs, rabbits and humans. In addition, human blood, HEK293 cells, hepatic microsomes and hepatocytes were utilised for *in vitro* PK assessment. Analytical methods used in the PK studies for determination of nalmefene and/or metabolites were validated and the main parameters of these methods were assessed and considered adequate.

Absorption

For the *in vivo* studies oral administration of nalmefene was used, which is the intended route for human use. Based on measurement of radioactivity after oral administration of ^{14}C -nalmefene, rapid

absorption with rather high bioavailability was observed in rats and dogs, whereas in humans only moderate bioavailability was found.

Distribution

Nalmefene is widely distributed, with the highest values found in liver, kidney and pancreas. It crosses the placental barrier and binds to melanin. In nursing rats, it was found in the milk at concentrations 3 times that of plasma 1 h post dose, but decreased to half the plasma concentration by 24 h post-dose. Only trace amounts were detected in the brain.

Metabolism

Nalmefene is extensively metabolized, the main metabolites being nornalmefene, nalmefene-3-O-glucuronide, nalmefene-3-O-sulphate and nornalmefene-3-O-glucuronide. The metabolizing enzymes for nalmefene have been characterized as CYP3A4/5 for the conversion of nalmefene to nornalmefene and UGT2B7 (major metabolite, see section 2.4.2), UGT1A3, UGT1A8 for the glucuronidation of nalmefene to nalmefene-3-O-glucuronide. The results of the metabolism studies revealed that both rats and dogs are suitable species for the safety evaluation of nalmefene.

Excretion

Only 5 – 14% of the parent compound was found in urine and faeces. The metabolic profile was similar in rats, dogs and humans, with the rat being closest to humans. No significant gender differences (rats, dogs) were observed. In rats and dogs, the faecal elimination represented the main route of excretion of drug related material, whereas in humans renal elimination was higher than the faecal excretion.

Drug-drug interactions

Data indicate a very low probability of metabolic interactions of nalmefene and its major metabolites via both CYP450 and UGT. Data presented suggest that nalmefene is neither a substrate for the human multi-drug resistance transporters (MDR1, BCRP, MRP2, organic anion transporter polypeptides OATP1B1, OATP1B3, and OCT1) nor does it inhibit these transporters.

2.3.4. Toxicology

Single dose toxicity

In single-dose studies, nalmefene was administered by the oral, iv and sc route to mice, rats and rabbits of both sexes. The respective oral LD50 values were 230 and <200 mg/kg for male and female mice, <300 and 150 mg/kg for male and female rats and <225 and 225 for male and female rabbits. Toxic signs in the lower doses included unsteady gait, decreased activity, arched back and tremors; convulsions, prostration and loss of balance / righting reflex were seen with higher doses.

Repeat dose toxicity

Chronic toxicity studies were performed in mice, rats, rabbits and dogs. For pivotal repeat-dose toxicity studies in rats and dogs were used, since, with respect to their metabolic pattern, these species cover the human situation in an acceptable manner. Treatment with up to 52 weeks with sufficient high oral doses of nalmefene resulted in rather minor clinical signs.

Rats treated over 52 weeks with nalmefene did not develop clinical signs of toxicity at the doses tested. The only symptoms seen in rats after 300 mg/kg were a moderate decrease of body weight gain concomitantly with reduction of food consumption. Some parameters of haematology, serum chemistry and urine analysis were slightly changed. However, since the effects were neither dose-related nor time-related, no specific concern was identified. There were some statistically significant differences in organ weights (heart, lung, liver, spleen) between nalmefene-treated groups and controls, but neither macroscopic nor histopathological examination revealed striking changes. However, some minor and insignificant increases in the rate of nephrocalcinosis in the kidneys in high dose females and cortical hyperplasia in the adrenals of mid and high dose females were seen. Therefore, no target organs were identified in this species. The NOAEL after 52 weeks treatment was set at an oral dose of 300 mg/kg.

Dogs treated with nalmefene for 52 weeks showed some clinical signs of toxicity (salivation, hypoactivity, hyperactivity, tremor and convulsions (16 and 64 mg/kg/day). Additionally, haematological analysis showed a trend towards haemoconcentration, increase in mean cell haemoglobin concentration (MCHC) and reductions in platelets. The NOAEL for this study was set at 4 mg/kg. Since no histopathological findings were found, no target organ in dogs could be defined.

Although neither rats nor dogs showed any changes in the liver after repeated administration of nalmefene, dose-dependent changes has been observed in the liver of male and female mice: in two studies both an increase in mean liver weight (33 – 69%) and periportal hepatocellular hypertrophy with minor foci of single cell or focal necrosis were described. Although no scientific explanation for these marked effects is available at present, it seems justified to consider this as a species-specific phenomenon.

The pivotal repeat-dose toxicity studies were performed in compliance with GLP requirements according to the respective guidelines.

Genotoxicity

From the submitted *in vitro* and *in vivo* genotoxicity studies, and mainly based on the overall data including lack of carcinogenicity of the compound, it can be concluded that nalmefene has no relevant genotoxic potential.

Carcinogenicity

Long-term carcinogenicity studies in rats and mice with nalmefene did not provide evidence for a carcinogenic potential of nalmefene at doses up to 100 mg/kg/day.

Reproduction Toxicity

With regard to reproductive toxicity, in two studies conducted in rats (fertility and early embryonic development, and combined fertility/pre- and postnatal development study) male and female fertility as well as early embryonic development was unaffected by oral treatment with nalmefene

hydrochloride up to 200 mg/kg/d, a dose which induced mortality, CNS toxicity and adverse effects on body weights in the parental generation. After dose reduction from 200 mg/kg/d to 100 mg/kg/d at the end of the mating period in the combined fertility/pre- and postnatal development study, no CNS toxicity was observed any more. Male rats appeared to be more sensitive to nalmefene hydrochloride as body weight gain was already adversely affected at the mid dose group (20 mg/kg/d) in the fertility and early embryonic development study.

When nalmefene hydrochloride up to 200 mg/kg/d was administered orally to pregnant rats during the period of organogenesis, embryofoetal development was not affected and the safety margin was 32 to 38 times the human AUC after the recommended maximum daily dose of 18.06 mg/kg.

The oral administration of nalmefene hydrochloride up to 200 mg/kg/d to pregnant rabbits during the period of organogenesis induced only slight materno-toxicity, but induced significantly decreased foetal body weights and increased skeletal variations indicating retardation of foetal development.

Another prenatal development study with intravenous administration of nalmefene hydrochloride was conducted in rabbits. The high dose of 8 mg/kg/d was clearly materno-toxic and in two doses (one of the mid and one of the high dose each) ascites was noted at necropsy. This finding was considered to be treatment-related revealing a maternal NOAEL of 0.25 mg/kg/d. Embryofoetal development after intravenous administration was only affected at the high dose of 8 mg/kg/d (slight increase in the number of does with all conceptuses resorbed, significant increase in foetal and litter incidence for skeletal variations) and the NOAEL was set at 1.25 mg/kg/d. When calculation of the safety margin for prenatal development is based on dose per kg body weight, a safety margin of 4.2 would exist.

No treatment-related teratogenicity was observed in either species.

In rats, data from the combined fertility/pre- and postnatal development study as well as from a peri- and postnatal development study were available. In both studies materno-toxicity, an increase in number of dams with stillborn pups and a decrease in pup survival were observed at the high dose of 100 mg/kg/d. Whilst the decrease in pup survival is likely due to maternal neglect, the cause of the increase in dams with stillborn pups is unknown.

When neonatal rats were dosed with nalmefene hydrochloride from birth until weaning with doses up to 50 mg/kg/d subcutaneously, no effects on body weights, viability, lactation, and cumulative survival index were noted and developmental milestones were not affected either. Histopathological examination revealed no drug-related effects, as the findings were seen in all groups including the control group without any dose-dependent increase.

Toxicokinetic data

The toxicokinetic profile of nalmefene was determined within the pivotal toxicology studies or in separate studies in mice, rats and dogs. In most cases, plasma concentrations of nalmefene and its metabolites nornalmefene, conjugated nalmefene (i.e. the sum of nalmefene glucuronide and nalmefene sulphate) and conjugated nornalmefene (i.e. the sum of nornalmefene glucuronide and nornalmefene sulphate) were determined. Both in rats and dogs the parent compound nalmefene was only detectable within the first hour in animals treated with high doses. In rats and dogs, the levels of the main metabolites nornalmefene, nalmefene glucuronide and nornalmefene glucuronide were much higher compared to nalmefene, suggesting rapid metabolism of the parent drug. No accumulation of nalmefene and/or metabolites could be observed after 52 weeks of administration.

In summary, the toxicokinetic parameters show that the metabolic profile of rats and dogs is similar to the profile observed in humans. Therefore, repeat dose studies in rats and dogs are relevant for safety

assessment. The toxicokinetic parameters are similar with respect to dogs and humans, but different between rats and humans.

The calculation of the safety margins for male and female fertility was based on mean plasma concentrations that were obtained for proof of absorption of the drug substance. At the NOAEL for fertility (200 mg/kg/d) safety margins were 64 to 244 times the human C_{max} after the recommended maximum daily dose of 18.06 mg.

At the developmental (rabbit study) NOAEL of 10 mg/kg/d no safety margin exists (AUC: 35.29 – 39.46 ng*h/ml compared to AUC of 131 ng*h/ml after maximum human daily dose of 18.06 mg nalmefene).

The developmental NOAELs in both studies performed in rats were similar (20 mg/kg/d and 15 mg/kg/d, respectively). When calculation of the safety margin for developmental toxicity is based on mean plasma concentrations that were obtained for proof of absorption of the drug substance in the combined fertility/pre- and postnatal development study, exposures were 15 to 18 times the human C_{max} after the recommended maximum daily dose of 18.06 mg.

Local Tolerance

Local tolerance *in vitro* and *in vivo* studies were carried out as required. Taking into account the intended route of administration under clinical conditions the results of the local tolerance studies did not indicate any concerns.

Other toxicity studies

Antigenicity was evaluated *in vivo* in mice and guinea pigs. There was no evidence to suggest that the test material, nalmefene, acts as sensitizer. Therefore, nalmefene was not regarded as allergenic. Nalmefene may have the potential for induction of allergic contact dermatitis. However, taking into account the intended route of administration under clinical conditions this is not a concern.

The potential dependence liability of nalmefene was tested in three different tests. It was shown that the drug acts like a powerful opioid antagonist without any agonistic activity. The drug is free of physical dependence liability and therefore unlikely to be abused.

Since bisnalmefene was found to be a potential degradation product of nalmefene, the acute intravenous toxicity of the substance has been tested in mice. The median lethal dose was 133.6 mg/kg, which reflects a considerably lower toxicity than that for nalmefene.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant provided a Phase I and Phase II Environmental Risk Assessment according to the guideline EMEA/CHMP/SWP/4447/00 corr 1 (June 2006).

Phase I - PBT-Screening

The applicant provided data on the octanol-water partition coefficient indicating that the trigger value of 4.5 for log K_{ow} is not exceeded. Hence, no further screening for PBT is necessary.

Phase I – PEC Calculation

The applicant conducted a refinement of the F_{pen} on prevalence data for alcoholism in Europe. The PEC was calculated with the refined F_{pen} of 3.79 % and a maximum daily dose of 18.06 mg/d*inhab. The

calculated $PEC_{\text{surfacewater}}$ for nalmefene is 0.342 $\mu\text{g/L}$ (free base) and exceeds the action limit of 0.01 $\mu\text{g/L}$. A Phase II assessment has been performed.

The results of the conducted fate and effect studies are summarized in the following table:

Table 1. Summary of main study results

Substance (INN/Invented Name): Nalmefene					
CAS-number (if available): 55096-26-9 (base)					
PBT screening		Result		Conclusion	
Bioaccumulation potential I-log K_{ow}		Following OECD 122		logD = 1.3 at pH = 7.4	
logD = 1.3 at pH = 7.4		Potential PBT: No			
Phase I					
Calculation		Value		Unit	
PEC _{surfacewater} (based on refined F _{pen} value)		0.34 (based on the free base with a molecular weight of 339.4 g/mol)		µg/L	
Other concerns (e.g. chemical class)				none	
Phase II Physical-chemical properties and fate					
Study type		Test protocol		Results	
Adsorption-Desorption		OECD 121		K _{oc} = 17783	
Adsorption-Desorption		OECD 106		K _{oc} = 78-1,756 L/kg (Soil) K _{oc} = 81-100 L/kg (Sludge)	
Ready Biodegradability Test		OECD 301		0% (28 d)	
Aerobic Transformation in Aquatic Sediment Systems		OECD 308		DT ₅₀ water: 0.7-1.4 d DT ₅₀ whole system: 6.2-14.1 d DT ₅₀ sediment: 70.4-187.6 d Sediment shifting: 27.8-39.4 % (at 14 d) Mineralisation: 2.7-4.9% (at 100 d) Bound residues: 45.6-57.7% (at 100d)	
Phase IIA Effect studies					
Study type		Test protocol		Endpoint	
Algae, Growth Inhibition Test		OECD 201		NOErC	
Daphnia sp. Reproduction Test		OECD 211		NOEC	
Fish, Early Life Stage Toxicity Test		OECD 210		NOEC	
Activated Sludge, Respiration Inhibition Test		OECD 209 (2010)		NOEC	
Phase IIB Effect studies					
Sediment – water toxicity test		OECD 218		NOEC	
		50*		mg/kg	
				Chironomus riparius	

* The test material was supplied as the salt (nalmefene HCl dihydrate) with a molecular weight of 411.9 g/mol. All test concentrations and results have been based on the free base nalmefene with a molecular weight of 339.4 g/mol.

Based on the above risk quotients and results, it was concluded that nalmefene is unlikely to bioaccumulate to a significant extent. The PEC/PNEC coefficients for algae, daphnia, fish and sediment dwelling organisms indicate that nalmefene is unlikely to present a risk to surface water. Furthermore, nalmefene does not absorb much neither to sewage sludge nor to soil. Hence, nalmefene is likely to remain mainly in the aqueous phase. There is no risk for sediment dwelling organisms. Due to the very low adsorption to sludge, an environmental risk assessment for the terrestrial compartment was not required.

In summary, it was concluded that, based on a maximum daily dose of 18.06 mg nalmefene hydrochloride, the prescribed usage of nalmefene is unlikely to represent a risk for the aquatic or terrestrial environment.

2.3.6. Discussion on non-clinical aspects

Comprehensive *in vitro* studies have shown that nalmefene is a selective opioid receptor ligand without any significant affinity to targets apart from opioid receptors. On the opioid receptor subtypes nalmefene has equal high affinity for μ , and κ opioid receptors respectively, and medium affinity for δ opioid receptors.

In contrast to the *in vitro* studies nalmefene acts clearly as a μ opioid antagonist without any agonistic activity under *in vivo* conditions.

Overall, the data demonstrate that nalmefene is an opioid system modulator with a distinct profile on μ , κ , and δ opioid receptors without any significant affinity to targets apart from opioid receptors. Accepted animal models of alcohol dependence, showed that nalmefene effectively suppresses voluntary alcohol intake even after repeated administration. The results of the safety studies do not raise concerns.

The pharmacokinetics of nalmefene have been investigated and the scientific quality of the studies is considered adequate. The studies conducted confirmed that both rats and dogs are suitable species for the safety evaluation. With respect to the pharmacokinetic properties, it was concluded that nalmefene met the requirements to support this Marketing Authorisation application.

Repeat dose toxicity studies were performed in mice, rats, rabbits and dogs. The toxicokinetic parameters are similar with respect to dogs and humans, but different between rats and humans.

From the submitted *in vitro* and *in vivo* genotoxicity studies, it could be concluded that nalmefene has no relevant genotoxic potential.

Long-term carcinogenicity studies in rats and mice with nalmefene did not provide evidence for a carcinogenic potential of nalmefene at doses up to 100 mg/kg/day.

With regard to reproductive toxicity, in two studies conducted in rats (fertility and early embryonic development, and combined fertility/pre- and postnatal development study) male and female fertility as well as early embryonic development was unaffected by oral treatment with nalmefene hydrochloride up to 200 mg/kg/d. After dose reduction to 100 mg/kg/d at the end of the mating period in the combined fertility/pre- and postnatal development study, no CNS toxicity was observed any more.

Oral administration of nalmefene hydrochloride up to 200 mg/kg/d to pregnant rabbits during the period of organogenesis induced only slight materno-toxicity, but induced significantly decreased foetal body weights and increased skeletal variations indicating retardation of foetal development.

No treatment-related teratogenicity was observed in either rats or rabbits.

With regards to the environmental risk assessment, nalmefene is unlikely to bioaccumulate to a significant extent and is unlikely to present a risk to surface water. Furthermore, Nalmefene does not much adsorb neither to sewage sludge nor to soil. It was concluded that, based on a maximum daily dose of 18.06 mg of nalmefene, the prescribed usage of the nalmefene is unlikely to represent a risk for the aquatic or terrestrial environment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of nalmefene have been adequately documented and meet the requirements to support this application. All issues related to pharmacology, pharmacokinetics and toxicology were resolved.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant provided a statement to the effect that parts of the clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. Several of the other studies were initiated before to the Directive came into force. These studies were conducted according to the principles of the "Declaration of Helsinki".

2.4.2. Pharmacokinetics

Nalmefene 18 mg IR tablets are to be taken as needed, i.e. on each day the patient perceives a propensity to drinking alcohol, as a single one-tablet dose, preferably 1-2 hours prior to the anticipated time of drinking. Available *in-vitro* biopharmaceutical, as well as *in-vivo* and modelling PK data support the proposed on-demand dosing schedule.

Absorption

Nalmefene is highly water-soluble, the proposed IR tablets rapidly dissolve *in-vitro* and display a rate and extent of absorption of nalmefene, that is equivalent to an oral solution formulation. After ingestion of a single 18 mg tablet, mean maximum plasma concentrations of 16.5ng/mL (22.3ng/mL after multiple days of single daily doses) are achieved after 1.5 hours with an AUC_{0-inf} value of about 130ngh/mL (AUC_{0-tau} after multiple doses 154ngh/mL, Integrated PK analysis Study 14019A).

Food effect

Results on the influence of food on nalmefene's absorption are somehow inconsistent. Ingestion of food (standardised meal, however, not high-fat according to guideline provisions) delayed achievement of maximum plasma concentration by about one hour (from 1.35 to 2.33h) and increased the overall extent of absorption by about 19% (3x18.06 mg doses, Study IX313-003). Additionally, in food study CPH-101-1302, delivery of NMF after food ingestion was increased. After ingestion of a high-fat meal plasma peak concentrations increased by about 50% and the extent of absorption (AUC) increased by

about 30%. Peak plasma concentrations were attained about 30 minutes later as compared to the fasted state (1 vs 1.5 h). However, there was no significant difference between the fed and fasted condition observed in Japanese volunteers in study 13505A. Overall, data on the influence of food do not point to a significant food effect requiring particular dosing recommendations for nalmefene. In the SmPC (Section 4.2), Selincro is to be taken with or without food (which is concordant with the method of administration in the pivotal phase III studies).

Distribution

Nalmefene is extensively metabolised. The biotransformations include hydroxylation, N-dealkylation, glucuronic acid conjugation, and sulphation. The primary enzyme responsible for conversion to the major metabolite nalmefene 3-O-glucuronide is UGT2B7. A small portion of nalmefene is converted to nornalmefene (de-alkylated nalmefene) mainly through CYP3A4/5. Nornalmefene is then further converted to nornalmefene 3-O-glucuronide and to nornalmefene 3-O-sulphate.

Nalmefene 3-O-glucuronide, nornalmefene, nornalmefene 3-O-glucuronide, and nornalmefene 3-O-sulphate have less affinity (26 to 1100 times lower) for the opioid receptors than the parent compound. The nalmefene 3-O-sulphate metabolite is considered to have potency comparable to that of nalmefene on the opioid receptors. However, since this metabolite is present in concentrations of less than 10% of that of nalmefene, it is considered unlikely that the nalmefene 3-O-sulphate metabolite be a major contributor to the pharmacological effect of nalmefene in humans

Elimination

Following administration of a single dose of 18 mg ¹⁴C-nalmefene to healthy subjects in distribution study 12393A, renal excretion represented the main route of elimination, with a mean of 71% of total radioactivity excreted in urine compared to a mean of 20% in faeces. Nalmefene 3-O-glucuronide was the major metabolite in urine, accounting for approximately 54% of the administered dose, while only trace amounts of intact nalmefene (3%) were excreted in urine. Nornalmefene was the predominant metabolite in faeces. The elimination half-life is about 12.5 hours.

Dose proportionality and time dependencies

Study 14019A / Integrated PK analysis

An integrated database regrouping PK parameters from several studies with single or multiple dose administration, with different formulations and diverse doses has been created. In order to be able to compare the parameters between the differing studies, dose-normalization was carried out.

Special populations

Renal impairment

PK data for oral administration of 18 mg NMF tablets in subjects with varying degrees of renal impairment as compared to healthy subjects are not available. In study 22 (an early open-label, single-dose study), eight patients with end-stage renal disease (ESRD) were administered 1 mg NMF as i.v. bolus injection over 15 seconds on two occasions: one time the day after a haemodialysis session and once four hours before the next scheduled haemodialysis with a wash-out of 1-2 weeks in-between. Exposure to nalmefene-conjugates was largely increased in end stage renal impairment (AUC values more than eight times higher). De-conjugation (and consequently re-institution of pharmacological activity) of metabolites or parent compounds has been reported if conjugated molecules cannot be eliminated. Healthy subjects were not directly involved in study 22. Instead, healthy subject data were taken from study 21, conducted in 1993 in order to examine the influence of

hepatic impairment after 2 mg i.v. bolus administration of NMF. Selincro is contraindicated in patients with severe renal impairment. Based on the available data, differentiated dose recommendations or warning notes for various degrees of renal impairment could not be formulated. This is reflected in Sections 4.2 and 4.4 of the SmPC.

Hepatic impairment

The impact of hepatic impairment was examined in Study 12417A in patients with mild or moderate hepatic impairment, compared with healthy subjects. The systemic exposure to nalmefene, based on AUC_{0-inf}, was statistically significantly higher in subjects with mild or moderate hepatic impairment (1.5- and 2.9-fold higher, respectively) than in healthy subjects. Subjects with severe hepatic impairment were not included and have also been excluded from the pivotal phase III studies. Selincro is contraindicated in patients with severe hepatic impairment. Clear differentiated dose recommendations for patients with various degrees of hepatic impairment cannot be given based on the current database. This is reflected in Sections 4.2 and 4.4 of the SmPC.

Pharmacokinetic interaction studies

In-vitro interaction studies demonstrated that nalmefene did not induce enzyme activity or affect the mRNA levels of any of the CYP enzymes evaluated (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5) and showed no or little inhibitory potency (direct or time-dependent) towards any of the CYP enzymes tested.

The *in-vivo* alcohol interaction study 13513 did not point to a clinically relevant pharmacokinetic interaction between nalmefene and ethanol. The 90% CI for the geometric mean ratio was within the standard bioequivalence limits of 0.80 to 1.25 for the AUC_{0-t} and the AUC_{0-inf} of nalmefene as well as for the AUC_{0-t} and the C_{max} of ethanol. For the C_{max} of nalmefene, subsequent exposure to ethanol was associated with an increase of 23%. However, the interaction between NMF and ethanol was not examined over a range of increasing blood alcohol concentrations, but at a single fixed amount, i.e. after administration of 0.6 g/kg body weight. The C_{max} values (mmol/mL) of ethanol corresponded to a blood alcohol concentration (BAC) of approximately 0.5 to 0.6‰ for men and women. Hence, data for the interaction between NMF and larger ethanol quantities (heavy drinking) are not available.

2.4.3. Pharmacodynamics

Mechanism of action

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.

Primary pharmacology

Study CPH-101-0902

Study CPH-101-0902 was an open-label, two-period, single- and multiple-dose study (conducted by the former licensee Biotie Therapies Corp. in 2002) in 12 healthy young subjects. The objective was to characterise the pharmacokinetics and the μ -opioid receptor occupancy in the brain after a single dose and after 7 days of dosing of 18.06 mg nalmefene. Blood was sampled for the analysis of nalmefene,

normalmefene, and their conjugates after the single dose and after the last repeated dose, at matching time points, up to 72 hours post-dose. The mean pharmacokinetic parameters of nalmefene are summarised in the Panel below.

Panel 18 Pharmacokinetic Parameters of Nalmefene after Single or Repeated Dosing of 20mg Nalmefene – Study CPH-101-0902

	Single Dose	Repeated Dosing	Ratio ^a (90% CI)	p-value
AUC ^b (ng·h/mL)	144.8 (28.6)	136.5 (31.6)	0.93 (0.84, 1.04)	0.270
C _{max} (ng/mL)	21.94 (10.02)	28.51 (10.04)	1.36 (1.06, 1.74)	0.0475
t _{max} (h)	0.75 (0.5-3.0)	0.98 (0.5-2.0)	NC	1.000
t _{1/2} (h)	13.40 (3.13)	13.38 (1.63)	1.02 (0.91, 1.14)	0.783

Arithmetic mean (SD) data are presented for AUC, C_{max}, and t_{1/2}.
Median (range) data are presented for t_{max}.
NC = not calculated

a Ratio of geometric means (repeated dose/single dose)

b AUC_{0-inf} for single-dose data, AUC_{0-t_{max}} for repeated-dose data

Opioid receptor occupancy

In Study CPH-101-0902 the μ -opioid receptor occupancy in the brain after single and multiple dosing of 18.06 mg nalmefene was examined by performing positron emission tomography (PET) scans. One single 18.06 mg dose and repeated daily dosing of 18.06 mg nalmefene for 7 days resulted in very high occupancy at the μ -opioid receptors (94 to 100%) measured 3 hours post-dose. The decline in occupancy was similar for single and repeated dosing, and was clearly slower than the decline in the plasma concentration of nalmefene or metabolites. The high nalmefene occupancy (83 to 100%) persisted 26 hours after single and repeated dosing and the receptor occupancy was still above 50% 50 hours after dosing. Demonstration of rapid and long-lasting high μ -opioid receptor occupancy after single doses of nalmefene provides pharmacodynamic support for the proposed once-daily, as-needed dosing schedule on the one side, but has safety consequences on the other side. Concomitant administration of opioid analgesics is contraindicated, i.e. nalmefene is to be discontinued in case opioid analgesia is required (e.g. in elective surgery) and respective warning notes are in the SmPC to alert the treating physician in case of emergency situations.

Study CPH-101-0199

Study CPH-101-0199 was an early phase I proof-of-concept study, conducted in experienced recreational drinkers that did not fulfil the criteria for being categorised as being alcohol dependent. Participants went through three 4-hour drinking sessions with free access to a maximum of twelve drinks (8 g alcohol each). Before the first session (baseline) no drugs were administered, three hours before the following two experimental sessions two dose levels of nalmefene hydrochloride (20 mg or 60 mg) or 50 mg of naltrexone as a positive control were administered.

The number of included subjects was low (n=8 in each arm), therefore data should be interpreted cautiously. However, it appears that after a kind of adaption period (no significant reduction in the number of drinks in all four treatment arms in the first experimental session), alcohol consumption was markedly reduced in all three verum groups during the second experimental session. For NMF 20 mg, NMF 60 mg and NTX 50 mg the number of drinks declined from 11-12 in the first experimental session to 1-2 in the second experimental session. There was virtually no placebo response with regard to the number of drinks. Although the study was conducted under double blind conditions, it may be assumed that participants soon recognized administration of placebo tablets. This may also be reflected by the fact that none of the subjects randomized to the placebo group reported any AEs either during or after

the second experimental session, whereas gastrointestinal and CNS-related AEs occurred in all verum groups.

Contrary to the observed reduction in the number of drinks, no indication for differences in time to the first, second or third drink could be found when the treatment groups were compared with each other. There were no consistent statistically significant differences between the groups in the VAS scores for feeling of intoxication and pleasure measured before the first, second and third drinks, and no statistically significant differences between the treatment groups in the maxima and minima of changes from the first score during the baseline session.

Symptoms indicative of restless legs were reported by three subjects receiving nalmefene. This adverse event was not observed in earlier NMF studies.

Based on these early proof-of-concept data, it is concluded that nalmefene may reduce the number of drinks consumed by recreational drinkers in a social drinking situation. The fact that a number of subjects had unpleasant adverse events after the first experimental session, but none reported any adverse events after the drug-free baseline session probably affected the outcome of the second experimental session. It is yet unknown in how far tolerability of nalmefene improves in the course of longer treatment units.

Secondary pharmacology

QTc study BTT31-CD005

Study BTT31-CD005 was a randomised double-blind, parallel-group, placebo-controlled, moxifloxacin-controlled study, conducted at Parexel UK from November 2007 to July 2008, investigating the effects of nalmefene on cardiac repolarisation in healthy subjects.

A total of 249 healthy men and women completed the study. The subjects were randomly allocated to receive one of four treatments orally for 7 days: nalmefene hydrochloride 20mg/day; nalmefene hydrochloride 40mg/day for 2 days, followed by nalmefene hydrochloride 80mg/day for 5 days; placebo for 7 days; or placebo for 6 days, followed by moxifloxacin 400mg for 1 day. Blood for pharmacokinetic analysis of nalmefene and nornalmefene was sampled up to 24 hours after the last dose, and electrocardiograms (ECGs) were recorded during the dosing period and on Day 7 up to 24 hours post-dose. The Primary pharmacodynamic variable was the Placebo-adjusted time-matched mean change from baseline in QT interval based on an individual correction method (QTcI). The mean pharmacokinetic parameters and QTcI levels after repeated doses of 20 or 80mg nalmefene hydrochloride are summarised in the Panel below.

Panel 20 Pharmacokinetic Parameters and QT_{cI} Levels for Nalmefene following 20 and 80mg Repeated Doses – Study BTT31-CD005

Parameter	Nalmefene 20mg	Nalmefene 80mg	Ratio Nalmefene 20mg/Nalmefene 80mg
AUC _{0-24h} (ng·h/mL)	150.8 (37.3)	652.5 (24.3)	4.33
C _{max} (ng/mL)	20.6 (48.5)	91.2 (32.3)	4.43
t _{1/2} (h)	14.3 (32.4)	15.3 (36.9)	1.07
QT _{cI} (ms) (lower/upper 90% CI)	5.4 (1.52/9.37)	5.6 (1.61/9.52)	1.03
Arithmetic mean (SD) data are presented for AUC, C _{max} , and t _{1/2} .			

The lower limit of the 90% CI was above zero at 3, 6, 8, and 12 hours post-dose for nalmefene hydrochloride 20 mg versus placebo and at 1, 2, 6, 8 and 10 hours post-dose for the nalmefene hydrochloride 80 mg versus placebo comparison, demonstrating a small nalmefene QTcI prolongation effect. Based on the primary variable (QTcI) and mean time-matched changes from baseline on Day 7, the upper limit of the 90% CI fell below the 10 ms bound at all time-points post-dose. The study can therefore be classified as a “negative” thorough QT/QTc study as per definitions adopted in the current ICH E14 Guideline.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetic studies include early studies on intravenous preparations and later studies on the oral preparation which is the subject of this application.

Nalmefene is rapidly absorbed (t_{max} is 1.5 hours) after a single oral dose of 18 mg nalmefene (tablet), resulting in a mean C_{max} of 16.5ng/mL and a mean AUC_{0-inf} of 131ng·h/mL. The absolute oral bioavailability of nalmefene was 41%. Food increases the bioavailability to 53%, which is considered unlikely to be of clinical significance, considering the wide therapeutic index.

Following a single oral dose of 18 mg ^{14}C -nalmefene, the mean total recovery of drug-related material was 91% 240 hours post-dose, with excretion of drug-related material essentially complete (89%) 120 hours post-dose. Renal excretion represented the main route of elimination, with a mean of 71% (CV 3.7%) of total radioactivity excreted in urine compared to a mean of 20% (CV 2.6%) in faeces.

Metabolism by glucuronide conjugation is the primary mechanism of clearance for nalmefene, with renal excretion being the main route of elimination of nalmefene and its metabolites.

Nalmefene is extensively metabolised. The biotransformations include hydroxylation, N-dealkylation, glucuronic acid conjugation, and sulphation. It undergoes extensive and rapid metabolism to its major metabolite nalmefene 3-Oglucuronide.

The integrated pharmacokinetic analysis estimated the oral clearance of nalmefene to 169L/h, which is in line with the systemic clearance of nalmefene (CL) of 60.1L/h in the population pharmacokinetic modelling. The elimination half-life was estimated to 12.5 hours in the integrated pharmacokinetic analysis.

Overall, the pharmacokinetic profile of nalmefene was well characterised.

2.4.5. Conclusions on clinical pharmacology

Following a single oral dose, the systemic exposure to nalmefene, based on AUC_{0-inf}, was statistically significantly greater for subjects with mild or moderate hepatic impairment, than for healthy subjects with normal hepatic function (1.5 and 2.9 times, respectively). Systemic exposure is increased in patients with hepatic impairment. It was not possible to conclude on tolerability on the basis of the limited numbers of 16 patients with hepatic impairment administered 18 mg nalmefene orally.

Overall, there was a higher exposure to nalmefene and nalmefene conjugates in a very limited number of patients with ESRD administered 1mg intravenously. Oral nalmefene was not administered to patients with renal disease. Thus, it was also not possible to conclude on the tolerability of nalmefene in renal disease on the basis of the data provided.

The influence of hepatic and renal impairment on the pharmacokinetics of nalmefene after oral administration of 18 mg doses was not fully elucidated. Data on the use of nalmefene in patients with severe hepatic impairment are missing. Severe hepatic impairment may, however, be frequently

encountered in the target population. Selincro is contraindicated in patients with severe renal or severe hepatic impairment.

2.5. Clinical efficacy

2.5.1. Dose response studies and Main studies

The efficacy and tolerability of nalmefene in the treatment of alcohol dependence were evaluated in three randomised, double-blind, placebo-controlled phase III studies (two confirmatory 6-month efficacy studies and one 1-year safety study) sponsored by Lundbeck and 5 studies in alcohol use disorders conducted by a company called Biotie.

Overview of Clinical Studies in Alcohol Dependence and Alcohol-use Disorders

Five studies in alcohol-use disorders conducted by Biotie as part of a development programme suggested that nalmefene could be effective in reducing alcohol consumption and provided the rationale for the further development of the nalmefene 18 mg dose. Studies CPH101-0399 and 0299 explored fixed dose daily dosing strategies using doses of between 5mg and 40mg (of nalmefene hydrochloride). Data from these studies suggested that doses below 18 mg were less efficacious. However, no clear dose response relationship could be discerned in terms of the HDD endpoint.

Figure 1: Tabular Summary of Clinical Studies in Alcohol-use Disorders (Biotie Sponsored)

<i>Controlled studies</i>			
CPH-101-0801	28-week (+ 24-week run-out), randomised, double-blind, placebo-controlled, flexible-dose (10, 20 [target dose], or 40mg), as-needed dosing	159	236
CPH-101-0701	28-week, randomised, double-blind, placebo-controlled, flexible-dose (10, 20 [target dose], or 40mg), as-needed dosing	82	85
CPH-101-0299	12-week daily dosing + 40-week as-needed dosing extension, randomised, double-blind, placebo-controlled, fixed-dose (5, 20, or 40mg)	58	5mg: 61 20mg: 59 40mg: 59
CPH-101-0399	16-week, randomised, double-blind, placebo-controlled, fixed-dose (10 or 40mg), daily dosing	50	10mg: 50 40mg: 50
<i>Uncontrolled study</i>			
CPH-101-0400	52-week, open-label, flexible-dose (10, 20, or 40mg), as-needed dosing		60
Total		349	660
ITT = intent-to-treat			

Studies CPH-101-0701 and Study CPH-101-0801 were randomised, double-blind, placebo-controlled 28-week studies using a flexible-dose regime (10, 20 or 40mg of nalmefene hydrochloride), as-needed dosing and identified 18 mg as the target dose. The most recent of the five studies, Study CPH-101-801, was a 28-week phase III study with a 24-week Run-out Period. Statistical significance was achieved in this study with a difference of 3HDDs ($p = 0.0065$; treatment-by-time interaction) between placebo and nalmefene. Mean dose was 19.3mg nalmefene (as hydrochloride), and the proportion of patients in the nalmefene group who did not change their dose in Months 1 to 7 ranged from 57% to 66%. This suggested that 18 mg nalmefene was well tolerated and efficacious in this study population.

The studies were conducted in Finland, in the United Kingdom and in the United States, in patients with alcohol dependence or other alcohol-use disorders. The study designs were both double-blind and open-label, and the dosing was either as-needed or daily, with fixed (5, 10, 20, or 40mg) or flexible doses (ranging from 10 to 40mg) of nalmefene hydrochloride. A total of 1009 were included in these studies 349 of whom were treated with placebo and 660 of whom received nalmefene.

These studies provided support for the 18 mg nalmefene dose used in the three main studies in alcohol dependence conducted by Lundbeck listed in figure 2 below.

Figure 2: Summary of main efficacy studies in Alcohol Dependence (Lundbeck-sponsored)

Study	Study Design	Number of Patients in FAS	
		PBO	NMF
12014A	24-week (+ 4-week run-out), randomised, double-blind, placebo-controlled, fixed-dose (20mg), as-needed dosing	289	290
12023A	24-week (+ 4-week run-out), randomised, double-blind, placebo-controlled, fixed-dose (20mg), as-needed dosing	326	329
12013A	52-week, randomised, double-blind, placebo-controlled, fixed-dose (20mg), as-needed dosing	137	415
Total		752	1034

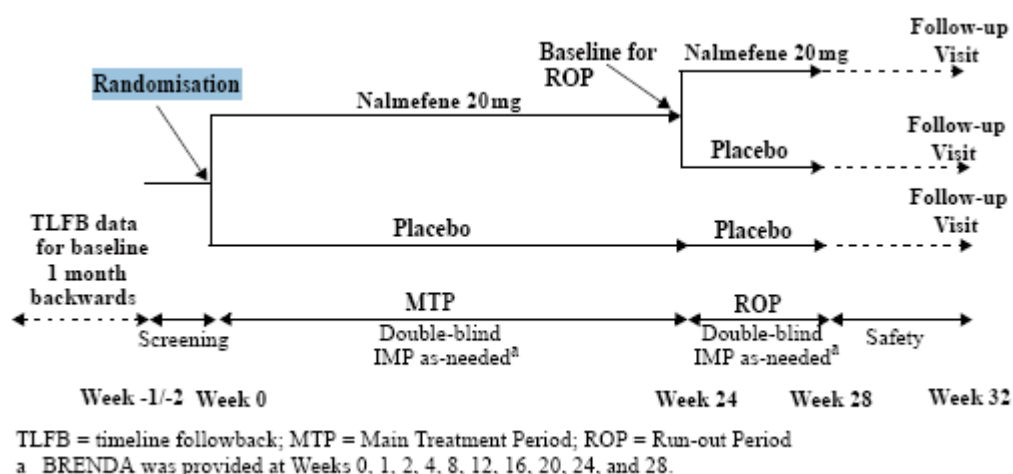
FAS = full-analysis set; PBO = placebo; NMF = nalmefene

In these studies, the patient population consisted of patients with a diagnosis of alcohol dependence according to the DSM-IV-TR criteria. The three studies were conducted in different regions in Europe to ensure that different drinking cultures were represented.

The 1-year study 12013A was primarily designed to collect long-term safety data on nalmefene to comply with the population exposure requirements for safety evaluation.

The two 6-month (24-week) efficacy studies 12014A and 12023A were of identical designs. For this reason their design is summarised in the same figure 3 below. Assessment of other aspects of these two studies is also dealt with together in sections of this assessment that follow.

Figure 3: Study Design – Studies 12014A and 12023A



Methods

The studies were conducted applying an outpatient setting without preceding detoxification. Higher CIWA withdrawal scores at Screening as well as a history of delirium tremens and seizures would be

indicative for the necessity of prior inpatient detoxification. Patients with abuse of substance other than alcohol and subjects with significant depressive or psychotic co-morbidity were excluded.

The studies included outpatients, aged ≥ 18 years, with a primary diagnosis of AD. A patient was eligible for participation in the study if, in the 4 weeks preceding the Screening Visit (Baseline period), he/she had ≥ 6 HDDs, at least a medium DRL, and ≤ 14 consecutive abstinent days. The timeline followback (TLFB) method was used to obtain estimates of the patient's daily drinking.

The studies were conducted over a 34 week period (12 visits) in total and consisted of four sequential periods: a 2-week screening period, a 24-week double-blind treatment period, a 4-week double-blind placebo-controlled run-out in each of the treatment arms and finally a 4-week safety follow-up. One to two weeks after the Screening Visit the patients were randomised 1:1 to 24 weeks of as-needed, double-blind treatment (Main Treatment Period; MTP) with nalmefene (18 mg) or placebo. The patients who completed 24 weeks of double-blind treatment entered a 4-week, double-blind Run-out Period (ROP). The patients randomised to nalmefene were re-randomised 1:1 to receive nalmefene (18 mg, as-needed) or placebo and the patients randomised to placebo continued on placebo.

The Timeline Follow-back (TLFB) method was used to collect self-reported drinking data (alcohol consumption).

The TLFB is a method to obtain estimates of daily drinking. Using memory aids, such as a calendar, patients provide retrospective estimates of the number of standard drinks for each day. A day was defined as a 24-hour period starting at 6.00 a.m. and ending at 6.00 a.m. the following morning. At the Screening Visit, each patient was to provide a retrospective estimate of his/her daily drinking over the previous month (a month was defined as a period of 28 consecutive days). At each subsequent visit, the patient was to provide information on his/her drinking since the previous visit. If a patient missed a visit, the TLFB that was completed at the next visit was extended to cover the days that should have been recorded at the missing visit. Patients could use their personal calendars to help them recalling their drinking or they could use a calendar provided by the site for their personal use. Calendars were only to be used as a memory aid to support the patients' input to TLFB. The patients were asked to report their alcohol intake by standard units according to the national definition of a standard unit. The standard national units were defined in standard drink conversion cards distributed to the patients.

The patients' alcohol intake (g/day) was estimated based on national definitions of standard units (subsequently converted into grams of alcohol). To define the standard units, a standard drink conversion card was distributed to each patient at the Screening Visit. Each patient was also provided with a calendar that he/she could use to support his/her input to the TLFB, or he/she could use a personal calendar, if preferred. For all the variables derived from the TLFB data, baseline was defined as the month (that is, 4 weeks /28 consecutive days) preceding the Screening Visit. The investigational medicinal product (IMP) was taken as-needed. Each patient was instructed to take a maximum of one tablet on each day the patient perceived a risk of drinking alcohol, preferably 1 to 2 hours prior to the anticipated time of drinking. If the patient had started drinking alcohol without taking IMP, the patient was to take one tablet as soon as possible. The dates when IMP was taken/not taken were recorded using the TLFB method. The chosen comparator was placebo, as there is currently no approved medicinal product for the reduction of alcohol consumption in patients with alcohol dependence.

All participants took part in a psychosocial programme (BRENDA) to enhance medication and treatment compliance at each visit. BRENDA, a motivational and adherence-enhancing intervention, was administered to all the patients throughout the treatment period in all three studies, in accordance with the EMA *Guideline on alcohol dependence*, which states that standardised psychosocial interventions should be allowed in alcohol dependence studies and kept to a constant and low level for all patients. BRENDA was administered using the accompanying manual, by trained site personnel (such as investigators, nurses, and psychologists) who were instructed to limit the sessions to approximately 15

to 30 minutes (except for the first session, administered at randomisation, which was approximately 30 to 40 minutes).

Studies 12014A and 12023A followed the same design. They were conducted in different European countries in order to reflect different regional patterns or traditions of alcohol drinking, as follows:

- Study 12014A (n=604) was conducted in Austria, Finland, Germany, and Sweden;
- Study 12023A (n=718) was conducted in Belgium, Czech Republic, France, Italy, Poland, Portugal and Spain.

Study Participants

The patients had a diagnosis of alcohol dependence diagnosed according to DSM-IV-TR. men and women, aged 18 years or over were included. A patient was eligible for participation in the study if, in the 4 weeks preceding the Screening Visit, he/she had:

- ≥ 6 HDDs
- at least a medium DRL
- ≤ 14 consecutive abstinent days

Alcohol dependence was diagnosed according to the DSM-IV-TR criteria, using the Mini International Neuropsychiatric Interview (MINI). Patients with other concomitant Axis I psychiatric disorders or significant somatic morbidity were excluded, as was any patient who was at risk of suicide, or who used substances of abuse (other than alcohol, cannabis, nicotine and benzodiazepines).

A patient was also excluded if he/she had (selected criteria are summarised below):

- withdrawal symptoms requiring medication (a Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar), Revised, score ≥ 10)
- a history of delirium tremens or alcohol withdrawal seizures
- a cognitive impairment that was likely to interfere with his/her understanding of the study and its procedures
- an aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) value >3 times the upper limit of the reference range, or a laboratory value outside the reference range (based on samples taken at the Screening Visit) that was clinically significant, as judged by the investigator
- clinically significant abnormal vital signs or electrocardiogram (ECG)
- current or recent treatment with antipsychotics or antidepressants. Furthermore, a patient had to provide a stable address and telephone number and an identified locator person.

Patients with a *high* or *very high* DRL are representative of patients with moderate or severe alcohol dependence in the general population and are the patients on which both the EMA Scientific Advice and the EMA *Guideline on alcohol dependence* place the most emphasis. However, patients with a *medium* DRL were also included in the studies, as the Applicant considered that these patients also have an increased risk of harm to their health.

The ratio of men to women was approximately 2:1. The patients in Study 12014A were slightly older (52 vs 45 years) and had a later onset of alcohol problems (38 *versus* 32 years) than the patients in Study 12023A. The majority (ranging between 65% and 75%) of the patients had a secondary education/high school education, or higher. At screening, approximately 60% of the patients were employed and approximately 60% of them were living with a spouse or partner.

Treatments

The IMPs were tablets of 18 mg nalmefene and placebo, identical in appearance, for oral administration. The IMPs were supplied in wallet cards. The wallet cards had space for the patients to record the date of IMP intake. All the tablets were manufactured, packaged, and labelled in accordance with the principles of Good Manufacturing Practice, under the responsibility of H.Lundbeck A/S.

In the studies conducted by the Applicant, all participants, including those allocated to placebo, received a motivational and adherence-enhancing intervention (BRENDA) throughout the treatment period. BRENDA is a psychosocial intervention consisting of the following six components 1) Biopsychosocial evaluation; 2) Report to the patient on assessment; 3) Empathic understanding of the patient's situation; 4) Needs collaboratively identified by the patient and treatment provider; 5) Direct advice to the patient on how to meet those needs; 6) Assess reaction of the patient to advice and adjust as necessary for best care. BRENDA was provided at week 0 (randomisation), 1, 2, 4, 8, 12, 16, 20, 24 (end of double-blind period), and week 28 (end of run-out period). The BRENDA approach is described in the literature (Starosta et al. 2006).

In Studies 12014A and 12023A, in conjunction with psychosocial intervention, the patients in the nalmefene group took IMP, on average, on 48% and 57% of the days, respectively, and the patients in the placebo group took IMP, on average, on approximately 65% of the days.

In the studies, the IMP was to be taken on an as-needed basis: the patient was instructed to take a maximum of one tablet each day the patient perceived a risk of drinking alcohol, preferably 1 to 2 hours prior to the anticipated time of drinking. If the patient had started drinking without taking IMP, the patient was to take one tablet as soon as possible. If there was no risk of drinking on a given day, the patient was not to take any IMP. The as-needed dosing schedule had no precedent in the pharmacologic treatment of AD.

The patients in both treatment groups adhered to the as-needed dosing regimen on approximately 80% to 90% of the days.

Objectives

- Primary Objectives

The overall objective of the study 12023A was the same as for Study 12014A, i.e. to evaluate the effect of as-needed dosing of 18.06 mg nalmefene on alcohol consumption in patients with alcohol dependence during a 24-week treatment period.

- Secondary Objectives

- to evaluate the effect of as-needed use of 18 mg nalmefene in patients with alcohol dependence during a treatment period of 24 weeks on:
 - proportion of responders based on various drinking measures
 - alcohol dependence symptoms and clinical status
 - liver function and other clinical safety laboratory tests
 - pharmacoeconomic outcomes
- to evaluate treatment withdrawal effects after 24 weeks of as-needed nalmefene treatment
- to evaluate the safety and tolerability of as-needed use of 18 mg nalmefene in patients with alcohol dependence
- to explore how genotype may affect treatment response to nalmefene

Outcomes/endpoints

Primary endpoints

The changes from baseline to Month 6 in number of Heavy Drinking Days (HDDs) and Total alcohol consumption (TAC) were defined as the two co-primary efficacy endpoints, as follows:

1. Number of HDDs (defined as a day with alcohol consumption ≥ 60 g for men and ≥ 40 g for women)
2. Total alcohol consumption (TAC, defined as mean daily alcohol consumption in g/day over a month (= 28 days))

The WHO has defined risk categories for health problems based on the level of daily alcohol consumption and these categories were used to define response, as a measure of the clinical relevance of the reduction in alcohol consumption.

Secondary endpoints

In all studies, the key secondary endpoint was response at Month 6, where response was defined as a downward shift from baseline in WHO DRL (RSDRL for patients with a *very high* DRL at baseline, a shift to *medium* DRL or lower [two-category shift]; for patients with a *high* DRL at baseline, a shift to *low* DRL [two-category shift]; and for patients with a *medium* DRL at baseline, a shift to *low* DRL [one-category shift]), as summarised below:

- for patients with *Very High Risk* at baseline: Shift to *Medium Risk* or below;
- for patients with *High* and *Medium Risk* at baseline: Shift to *Low Risk* or below.

The risk levels are defined in the WHO '*International guide for monitoring alcohol consumption and related harm*':

DRL ^{a,b}	Total Alcohol Consumption (g/day)	
	Men	Women
Very high risk ^c	>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

a *International Guide for Monitoring Alcohol Consumption and Related Harm*¹⁶

b Unless otherwise noted, the risk applies to alcohol consumption on a single day in relation to acute problems and to chronic harm.

c The *very high* risk category does not exist for chronic harm.

Other secondary endpoints were:

- Responder analyses:
 - proportion of patients with $\geq 30\%$, $\geq 50\%$ and $\geq 70\%$ reduction from baseline I in monthly total alcohol consumption
 - RLDRL response (defined as a downward shift in DRL to *low risk* or below)
- no heavy drinking days (no HDDs) by month
- Number of non-drinking days (NDDs)
- Alcohol Dependence symptoms and clinical status at visits in the first 24-week treatment period.
- Change from baseline in Drinker Inventory of Consequences (DrInc), The DrInc is a self-administered 50-item questionnaire designed to measure adverse consequences of alcohol abuse in five areas: Interpersonal, Physical, Social, Impulsive, and Intrapersonal.

- Clinical Global Impression-Improvement (CGI-I)(clinician assessed), 7-point scale. 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse
- Change from baseline in Clinical Global Impression-Severity CGI-S, (Clinical Global Impression Severity Scale): 7-point scale. 1= normal, not at all ill; 2= borderline ill; 3= mildly ill; 4= moderately ill; 5= markedly ill; 6= severely ill; 7= among the most extremely ill patients
- Alcohol Dependence Scale (ADS total score) 25 items covering alcohol withdrawal symptoms, impaired control over drinking, awareness of a compulsion to drink, increased tolerance to alcohol, and drink-seeking behaviour.
- Liver function and other biological laboratory tests at visits in the first 24 weeks of treatment
 - Serum gamma-glutamyl transferase (s-GGT) serum alanine amino transferase (s-ALAT) mean corpuscular volume (MCV) carbohydrate-deficient transferrin (CDT)

Sample size

Based on previous clinical experience, Standard Deviations for the change from baseline HDD and the change from baseline TAC were found to be 7 days and 36.5 g/day, respectively. With a significance level of 5% for each of the tests, 300 patients per treatment group would therefore provide around 90% power for detecting treatment differences in both the two co-primary variables, in case the true differences would be 3 heavy drinking days and 12 g/day in the total consumption. This evaluation was calculated by simulation and assuming a correlation of 0.7 between the co-primary endpoints and dropout at month 6.

In study 12023A, the sample size was increased to 700 patients (350 patients in each treatment group) after a blinded review of the data indicated higher than anticipated standard deviations and lower than anticipated correlations for the co-primary endpoints. As this retrospective power analysis resulting in an increased sample was conducted prior to unblinding, it was acceptable to the CHMP.

Randomisation

Participants were randomly allocated to one of the treatment groups according to a randomisation list computer-generated by H. Lundbeck A/S. At each study site, the investigator was responsible for assigning the IMP in consecutive order, starting with the lowest number available.

Blinding (masking)

Two sets of sealed envelopes containing IMP details for each patient were prepared. One set was kept by each of the following: Global Pharmacovigilance, H.Lundbeck A/S, and the investigator or pharmacist. The randomisation code was to be broken by the investigator only in an emergency situation in order to give the patient optimal treatment.

The CHMP considered that pivotal 6-month placebo-controlled trials were all double-blind in study design. All participants were blinded to outcomes. The method for sequence generation in the randomisation process and the allocation concealment were adequate.

Statistical methods

Co-primary Efficacy Analyses

The Applicant defined various analysis populations:

1. All-patients-randomised set (APRS) – all randomised patients.

2. All-patients-treated set (APTS) – all patients in the APRS excluding those with no recorded IMP intake and all IMP returned.
3. Full-analysis set (FAS) – all patients in the APTS who had at least one valid post-baseline assessment.

Baseline characteristics, demographics, and concomitant medication were summarised for the APRS. Exposure was summarised for the APTS. All efficacy analyses were conducted on the FAS. All safety analyses were conducted on the APTS; pre-treatment adverse events were summarised for the APRS.

The co-primary analyses of efficacy were the changes from Baseline I in monthly number of HDDs and monthly TAC in the nalmefene group compared to the placebo group. Both co-primary efficacy variables concerned the treatment effect at Month 6. Superiority of nalmefene over placebo was tested at the 2-sided 5% significance level, with the null hypothesis being no difference between nalmefene and placebo, and the alternative hypothesis a difference between treatments.

The efficacy analyses were conducted on the *full-analysis set* (FAS). The primary analysis pre-specified for both co-primary efficacy variables was a mixed model repeated measures (MMRM) analysis using all available data measured over each month during the treatment period using a model with Baseline I score as covariate, site, sex, time and treatment as fixed effects, baseline-by-time and treatment-by-time interaction and an unstructured covariance matrix. The MMRM analysis provides an estimate of the treatment effect under the assumption that data are missing at random. Monthly observations were disregarded if there were <7 days of data.

Several sensitivity analyses (analyses of covariance (ANCOVAs) using observed cases (OC), last observation carried forward (LOCF) and baseline observation carried forward (BOCF)) were pre-specified to evaluate how different assumptions would influence the estimate of the treatment effect and the robustness of the results. Additional sensitivity analyses were pre-specified in the Statistical Analysis Plan for one of the 6-month efficacy studies (Study 12023A). These sensitivity analyses included placebo mean imputation (PMI) and multiple imputation with a pattern mixture model. Details of these sensitivity analyses are below:

- MMRM analysis in which monthly observations were disregarded if there were <14 days of data.
- Analyses of covariance (ANCOVA) by month with the Baseline I score as a covariate and site, sex, and treatment as fixed effects, using the OC, last observation carried forward (LOCF), or baseline observation carried forward (BOCF) method of imputation. For each month, treatment effects and the difference in treatment effects were estimated from the model. The estimates were presented with two-sided 95% CIs and corresponding p-values.
- ANCOVA analyses were performed (*post-hoc* for study 12014A) in which missing values were imputed using placebo mean imputation (PMI) based on the mean reduction observed at Month 1 in the placebo group (adjusted for sex).
- Multiple imputation analyses with a pattern mixture model were performed (*post-hoc* for study 12014A) assuming that the patients who drop out differ from completers and that the future behaviour of their outcomes (conditional on the past) is the same as those in the placebo group (with the same past).

Subgroup analyses of the number of HDDs and TAC in the Main treatment period (MTP) were performed for the patients *with* a high or *very high* DRL at Baseline I, using an MMRM model similar to that used for the primary efficacy analyses. In addition, post-hoc ANCOVA analyses were performed using LOCF for the patients with a *high* or *very high* DRL at Baseline I.

To address the observation that some patients started to reduce their alcohol consumption immediately after they had consented to participate in the study (i.e. at the Screening Visit), post-hoc analyses of the co-primary variables were performed to estimate the effect of nalmefene versus placebo in the patients who, at the time of randomisation, still fulfilled the requirements pre-specified

in the protocol regarding alcohol consumption for the Screening Visit. Based on TLFB data, the patients were classified as having (yes/no) at least a medium DRL and at least 6 HDDs in the period between screening and randomisation (extrapolated to 4 weeks). These analyses were performed using the primary MMRM model including alcohol consumption at randomisation (yes/no)-by-time-by-treatment interaction with randomisation score as response assuming no systematic difference between the treatment groups. ANCOVA analyses using LOCF were also performed including alcohol consumption at randomisation by-treatment interaction.

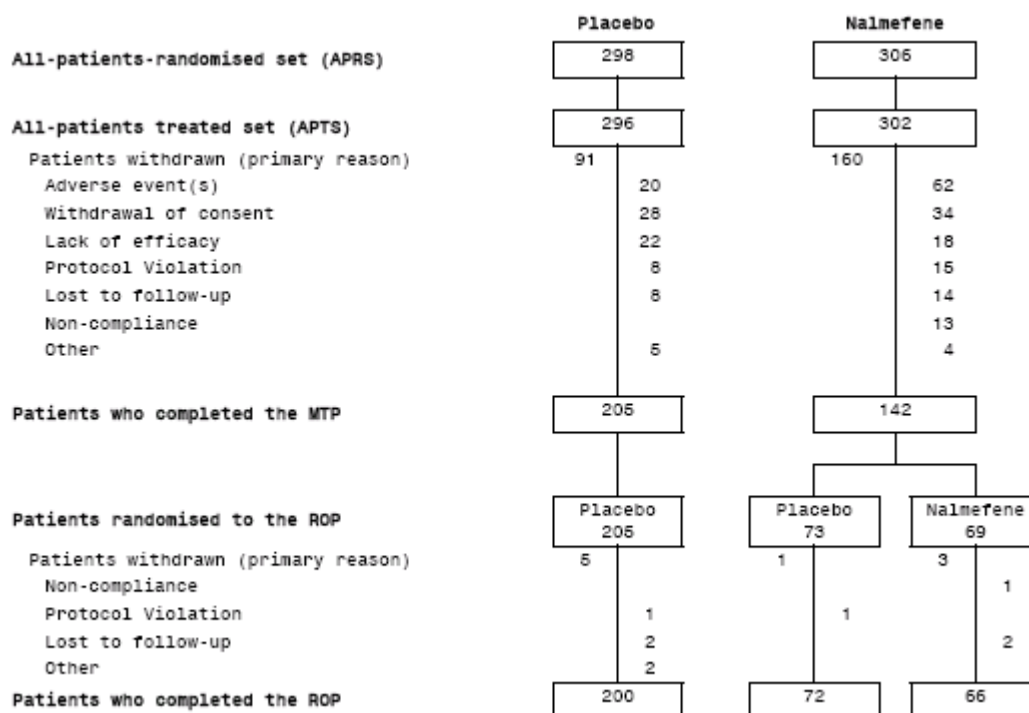
Key Secondary Efficacy Analysis

The key secondary analysis (RSDRL) was performed using a logistic regression (LREG) model. The same methods for handling missing data were applied in all three studies (missing values were imputed as non-response, using MMRM-predicted TAC, and using LOCF and LOCF sustained response), although the imputation method that was pre-specified for the key secondary analysis differed between Study 12014A and Studies 12023A. Prior to unblinding of any study, a Statistical Analysis Plan (Meta-analysis SAP) for a pooled analysis of the key secondary endpoint across the Lundbeck studies was issued. The Statistical Analysis Plan was amended twice: in the first amendment (Meta-analysis SAP 1), the analysis strategy was aligned with the overall strategy for analysing the co-primary variable TAC; in the second amendment (Meta-analysis SAP 2), which was issued prior to unblinding Study 12023A, the pooling of the two 6-month efficacy studies only was introduced.

Results

Participant flows

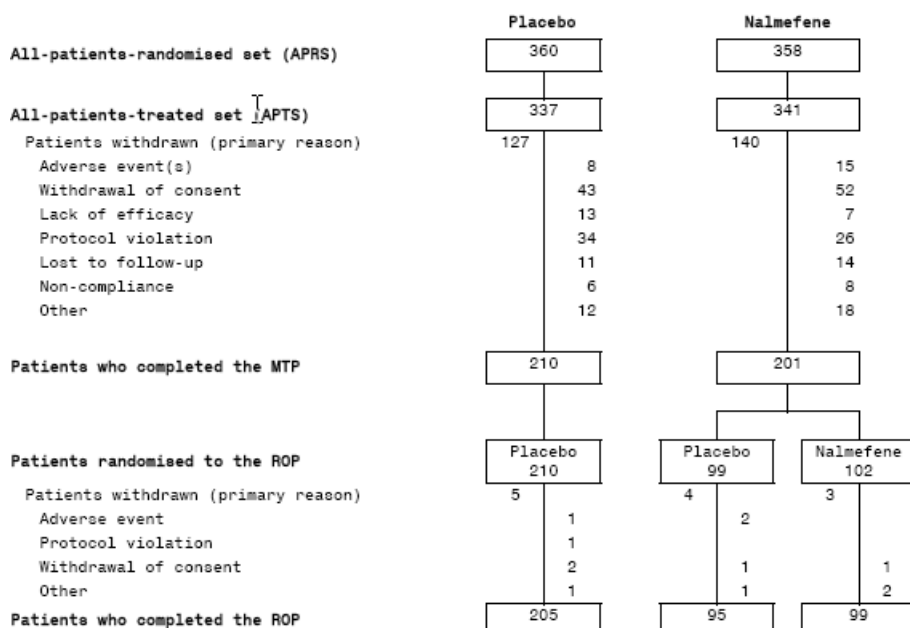
Participant flow Study 12014A



A total of 56% of the patients completed the study: 68% in the placebo group and 46% in the nalmefene group. During the MTP, 31% of the placebo-treated patients and 53% of the nalmefene-treated patients withdrew from the study; the most frequent primary reason for withdrawal was withdrawal of consent in the placebo group and adverse events in the nalmefene group. The proportion of patients with adverse events leading to withdrawal in the Main Treatment Period (MTP) was approximately three times higher in the nalmefene group than in the placebo group. The majority of all withdrawals occurred in the MTP, and almost all (>95%) of the patients in each treatment group who entered the ROP completed the period. In the MTP, time to withdrawal for any reason shows a pattern of earlier withdrawal in the nalmefene group than in the placebo group.

Overall 44% of participants withdrew, which was higher than the anticipated 35% withdrawal rate. In Study 12014A, the withdrawals occurred earlier in the nalmefene group than in the placebo group. There was a 22% higher withdrawal rate from the nalmefene group than the placebo group primarily driven mainly by a higher reporting rate of adverse events over the six month period. The numbers of participants withdrawing due to withdrawal of consent was high.

Participant flow for study 12023A



A total of 59% of the patients completed the study: 61% in the placebo group and 57% in the nalmefene group. During the MTP, 38% of the placebo-treated patients and 41% of the nalmefene-treated patients withdrew from the study; the most frequent primary reason for withdrawal was withdrawal of consent in the placebo and nalmefene groups. The proportion of APTS patients with adverse events leading to withdrawal in the MTP was approximately two times higher in the nalmefene group than in the placebo group. The majority of all withdrawals occurred in the MTP, and almost all (>95%) of the patients in each treatment group who entered the ROP completed the period. Approximately 51% and 27% of the patients in the placebo and nalmefene groups, respectively, who withdrew their consent did so in Month 6. Approximately 50% of the patients in the placebo and nalmefene groups who withdrew from the study due to protocol violations did so in Month 6 of the MTP; there were no other clear trends.

Overall 41% of participants withdrew. The patterns of withdrawal were similar for both nalmefene and placebo groups. The rate of withdrawal increased over the duration of the study. The majority of the participants withdrew because of withdrawal of consent or protocol violations. The rate of withdrawal due to adverse events was lower than in study 12014A.

Withdrawals (for Studies 12014A and 12023A)

Figure 4: Withdrawals by Primary Reason (FAS)

	12014A		12023A	
	PBO n (%)	NMF n (%)	PBO n (%)	NMF n (%)
FAS	289 (100)	290 (100)	326 (100)	329 (100)
Patients Completed ^a	213 (74)	152 (52)	229 (70)	212 (64)
Patients Withdrawn	76 (26)	138 (48)	97 (30)	117 (36)
Primary Reason				
Adverse events	17 (6)	57 (20)	4 (1)	12 (4)
Lack of efficacy	19 (7)	17 (6)	13 (4)	7 (2)
Non-compliance		7 (2)	3 (1)	7 (2)
Protocol violation	4 (1)	10 (3)	25 (8)	19 (6)
Withdrawal of consent	25 (9)	31 (11)	32 (10)	43 (13)
Lost to Follow-up	7 (2)	12 (4)	11 (3)	12 (4)
Other	4 (1)	4 (1)	9 (3)	17 (5)

^a Patients with TLFB data at Month 6

In Study 12014A, the proportion of patients who withdrew was higher in the nalmefene group than in the placebo group, whereas in Study 12023A, the proportion of patients who withdrew was similar in both treatment groups. The most common reason for premature discontinuation were adverse event and withdrawal of consent (withdrawals occurred earlier in the nalmefene group than in the placebo group in Study 12014A, primarily driven by the greater proportion of patients who withdrew due to adverse events in the nalmefene group than in the placebo group), whereas the time to withdrawal was similar in the nalmefene and placebo groups in Study 12023A. In each study, the patients who withdrew, in general, did not increase their alcohol consumption up to the time of withdrawal, irrespective of the reason for withdrawal. For the majority of the patients who withdrew, alcohol consumption was stable (or decreasing) up to the time of withdrawal. The majority of the withdrawn patients who became responders did so early in the course of treatment and did not subsequently shift to being a non-responder. In Studies 12014A and 12023A, the proportion of patients who withdrew and the time to withdrawal in the patients with a *high* or *very high* DRL at baseline were similar to those in the corresponding total population.

Recruitment

Study 12014A was conducted in 4 countries (over 39 sites – 4 in Austria, 11 in Finland, 16 in Germany, and 8 in Sweden between 18 December 2008 and 14 October 2010.

Study 12023A was conducted in 7 countries (over 57 sites – 7 in Belgium, 3 in the Czech Republic, 16 in France, 10 in Italy, 7 in Poland, 4 in Portugal, and 10 in Spain) from 16 March 2009 to 22 March 2011.

The study participants were recruited from in- and out-patient clinics, from the study sites' own patient pool, by referrals to the study site, or using advertisements. Advertisements were used in all the countries in 12014A and in 4 of the countries in 12023A.

Conduct of the studies

Although the studies were designed and conducted prior to the publication of the EMA Guideline on alcohol dependence the key elements of the study designs were in line with the recommendations of the EMA guidance. Each study was conducted as outlined in the protocol and subsequent amendments. The investigators were specialists and/or physicians with experience relevant to the studies.

The following protocol deviations in Study 12014A resulted in patients' exclusion from the full analysis set

- Patient 3557 was excluded from the FAS as the patient was randomised without any TLFB data for the 4 weeks preceding the Screening Visit.
- Patients 3054, 3059, and 3532 were excluded from the FAS as the patients had an average alcohol consumption ≤ 40 grams of ethanol/day in the 4 weeks preceding the Screening Visit

In Study 12023A, the following deviations resulted in the following patients being excluded from the FAS: Patients 3068, 3119, 3124, 3243, 3400, 3489, 3608, 3630, 3667, 3679, and 3911 were excluded from the FAS as the patients had an average alcohol consumption ≤ 40 grams of ethanol/day in the 4 weeks preceding the Screening Visit. An additional 4 patients (3010, 3164, 3353 and 3612) had < 6 HDDs in the 4 weeks preceding the Screening Visit but were randomised.

Baseline data

At baseline, approximately 80% of the patients in each of the studies had a high or very high DRL and approximately 20% of the patients had a medium DRL, which translated into a mean of approximately 20HDDs per month (out of 28 days per month) and a mean TAC of approximately 85 to 90g/day. At

baseline, the patients drank alcohol on most days, and both on weekdays and on weekends. It should be noted that only 4% of the patients had >7 consecutive non-drinking days/month at baseline. With their high level of alcohol consumption, the pattern of drinking in the total population was above and beyond any “normal” variations in cultural drinking patterns that exist across Europe.

Numbers analysed

Study 12014A included n=604 randomised patients (306 NMF + 298 PBO)

Study 12023A included n=718 randomised patients (358 NMF + 360 PBO)

Study 12013A included n=675 randomised patients (509 NMF + 166 PBO)

Total: 1997 (1173 NMF + 824 PBO)

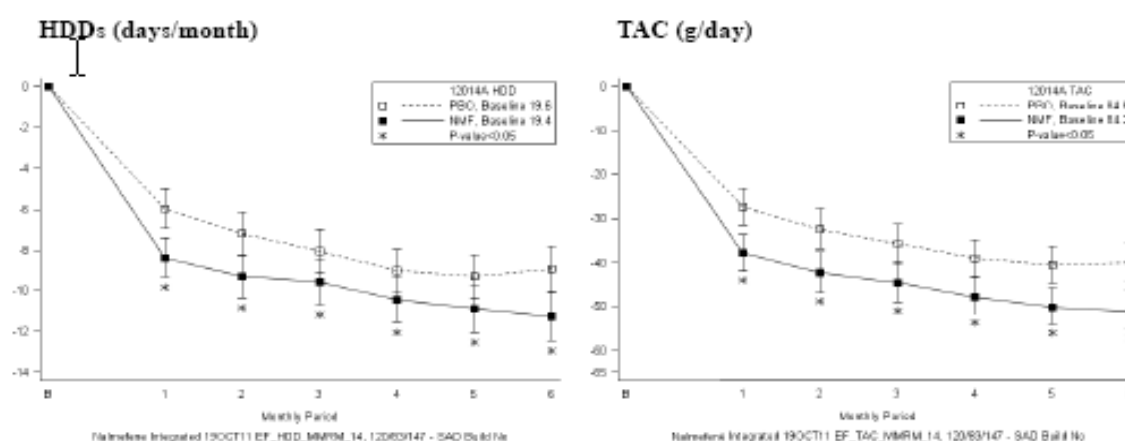
Outcomes and estimation

The main results of studies 12014A and 12023A and of Study 12013A are presented individually.

- Study 12014A

The co-primary efficacy analyses were the changes from Baseline I in monthly number of HDDs and TAC. Nalmefene was statistically significantly superior to placebo in reducing both the number of HDDs ($p = 0.002$) and TAC ($p < 0.001$) at Month 6. The effect of nalmefene was evident already at Month 1 and maintained throughout the MTP. In the nalmefene group, the mean number of HDDs decreased from 19 to 7 days/month and the mean TAC decreased from 84g/day to 30g/day at Month 6, a reduction of approximately 64%. In the placebo group, the mean number of HDDs decreased from 20 to 10 days/month and the mean TAC decreased from 85g/day to 43g/day at Month 6, a reduction of approximately 50%.

Changes from Baseline in HDDs and TAC (FAS, MMRM) – Study 12014A



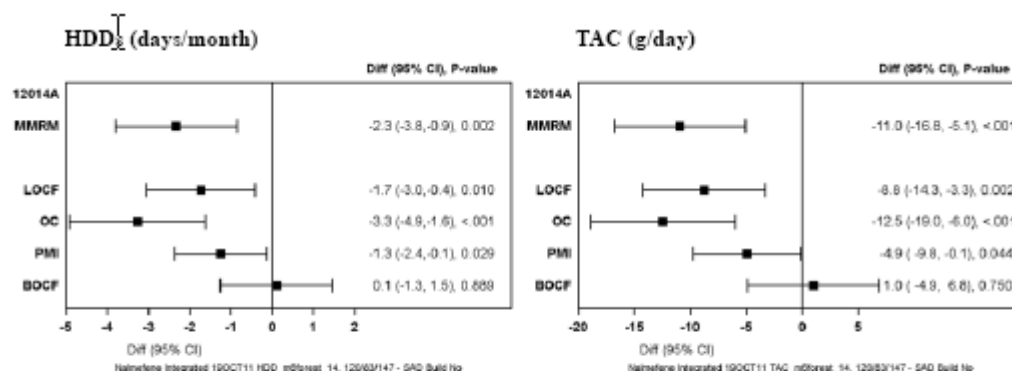
Results for the Co-primary Efficacy Variables at Month 6 (FAS) –Study 12014A

Variable Treatment Group	Baseline		Change from Baseline to Month 6		Difference to PBO		
	N	Mean ± SD	N	Mean ± SE	Mean ± SE	95% CI	p-value
Number of HDDs (days/month)							
MMRM							
PBO	289	19.6 ± 6.9	213	-8.9 ± 0.6			
NMF	290	19.4 ± 7.3	152	-11.2 ± 0.6	-2.3 ± 0.8	[-3.8; -0.8]	0.002
LOCF							
PBO	289	19.6 ± 6.9	289	-8.4 ± 0.6			
NMF	290	19.4 ± 7.3	290	-10.2 ± 0.6	-1.7 ± 0.7	[-3.0; -0.4]	0.010
TAC (g/day)							
MMRM							
PBO	289	85 ± 42	213	-39.7 ± 2.2			
NMF	290	84 ± 42	152	-50.7 ± 2.4	-11.0 ± 3.0	[-16.8; -5.1]	<0.001
LOCF							
PBO	289	85 ± 42	289	-37.7 ± 2.3			
NMF	290	84 ± 42	290	-46.5 ± 2.3	-8.8 ± 2.8	[-14.3; -3.3]	0.002

Baseline values are based on FAS, OC.

Additional analyses for Study 12014A

For each of the co-primary variables, the ANCOVA sensitivity analyses using LOCF, OC, PMI and BOCF were conducted. ANCOVA sensitivity analyses using LOCF, OC, PMI showed that nalmefene was superior to placebo. In the ANCOVA, BOCF analysis, the changes from baseline were similar in both treatment groups but with placebo being marginally more effective.



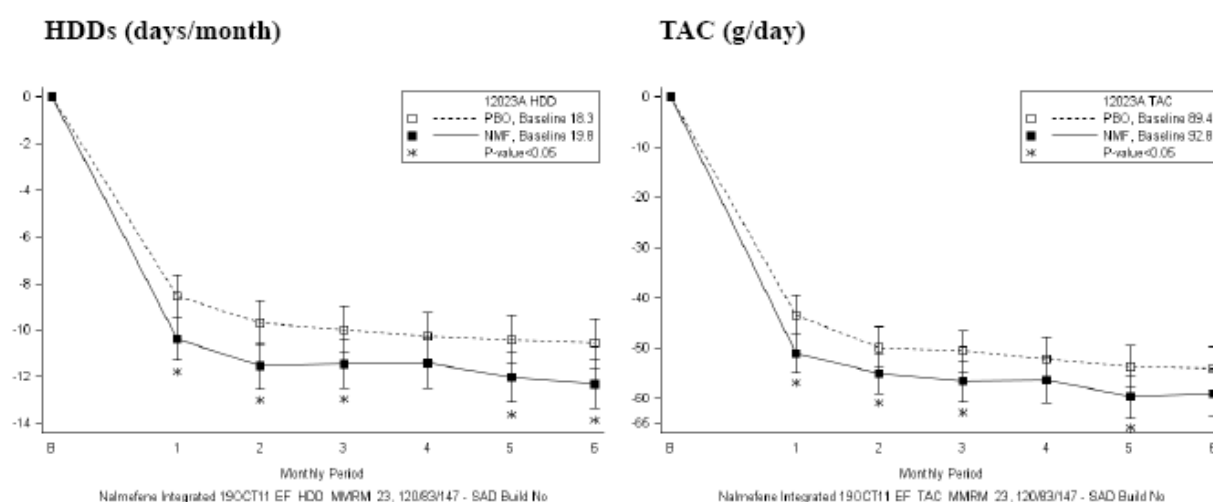
MMRM is the co-primary efficacy analysis and is included for comparison.
Negative values indicate a greater reduction in the number of HDDs and TAC in the nalmefene group than in the placebo group.

For the majority of the patients who withdrew, alcohol consumption was stable (or decreasing) up to the time of withdrawal. LOCF analysis could be considered to be conservative in this situation. Statistical significance was achieved in favour of nalmefene for this analysis, albeit the treatment effect estimate was small and clinical significance of a reduction of 1.7 HDDs and -8.8 g/day of alcohol was considered unclear.

- Study 12023A

The co-primary efficacy analyses were the changes from Baseline I in monthly number of HDDs and TAC.

Changes from Baseline in HDDs and TAC (FAS, MMRM) – Study 12023A



HDDs

Nalmefene was statistically significantly superior to placebo ($p = 0.012$) in reducing the number of HDDs at Month 6, with a mean difference to placebo of 1.7 days. At Baseline I, the mean number of HDDs was 18 in the placebo group and 20 in the nalmefene group. In the placebo group, the mean number of HDDs decreased to 10 at Month 1 and further to 7 at Month 6. In the nalmefene group, the mean number of HDDs decreased to 9 at Month 1 and further to 7 at Month 6. The reduction in the mean number of HDDs was in favour of nalmefene ($p < 0.05$) from month 1 and throughout the MTP (except at Month 4).

TAC

At Month 6, the mean reduction in TAC was numerically greater in the nalmefene group than in the placebo group, with a mean difference to placebo of 5g/day. The difference was not statistically significant ($p = 0.088$). The reduction in TAC was in favour of nalmefene ($p < 0.05$) from Month 1 and throughout the MTP (except at Month 4 and Month 6; In absolute terms at Baseline I, the mean TAC was 89g/day in the placebo group and 93g/day in the nalmefene group. In the placebo group, the mean TAC decreased to 46g/day at Month 1 and further to 33g/day at Month 6. In the nalmefene group, the mean TAC decreased to 39g/day at Month 1 and further to 30g/day at Month 6.

Results for the Co-primary Efficacy Variables at Month 6 (FAS) –Study 12023A

Efficacy Variable Treatment Group	Baseline I		Adjusted Change from Baseline I to Month 6		Difference to PBO		
	N	Mean \pm SD	N	Mean \pm SE	Mean \pm SE	95% CI	p-value
Number of HDDs							
PBO	326	18.3 \pm 7.0	229	-10.6 \pm 0.5			
NMF	329	19.8 \pm 6.8	212	-12.3 \pm 0.5	-1.7 \pm 0.7	[-3.1; -0.4]	0.012
TAC							
PBO	326	89 \pm 48	229	-54.1 \pm 2.2			
NMF	329	93 \pm 46	212	-59.0 \pm 2.3	-5.0 \pm 2.9	[-10.6; 0.7]	0.088

Baseline I values were based on FAS, OC; changes from Baseline I and differences to placebo were based on MMRM; FAS, OC values.

Cross-reference: Tables 37 to 40

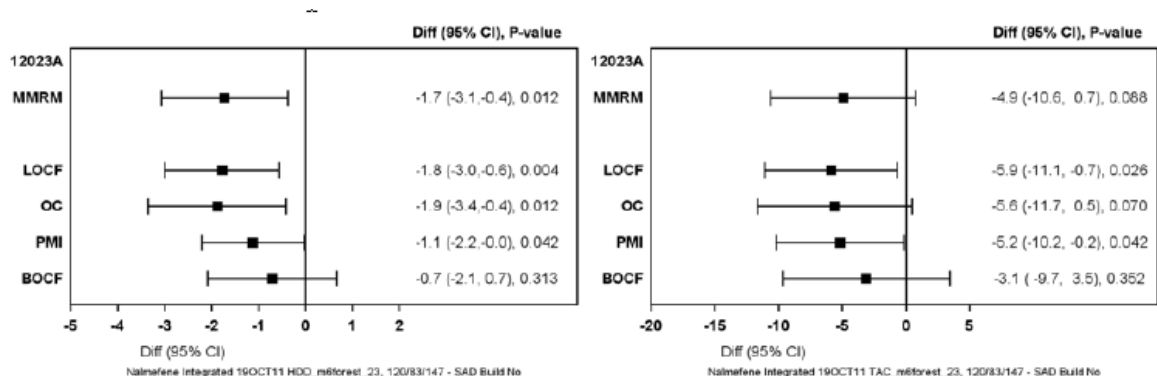
Additional analyses for Study 12023A

For each of the co-primary variables, all the ANCOVA sensitivity analyses using LOCF, OC, PMI, or BOCF were calculated. For HDDs the ANCOVA using OC, LOCF, or PMI showed that nalmefene was

statistically significantly superior to placebo. Statistical significance was not achieved for the BOCF analysis. An MMRM analysis in which Site BE006 was excluded gave results similar to those of the primary analysis.

Adjusted Changes from Baseline I in HDD:

Adjusted Changes from Baseline I in TAC



MMRM is the co-primary efficacy analysis and is included for comparison.
 Negative values indicate a greater reduction in the number of HDDs and TAC in the nalmefene group than in the placebo group.

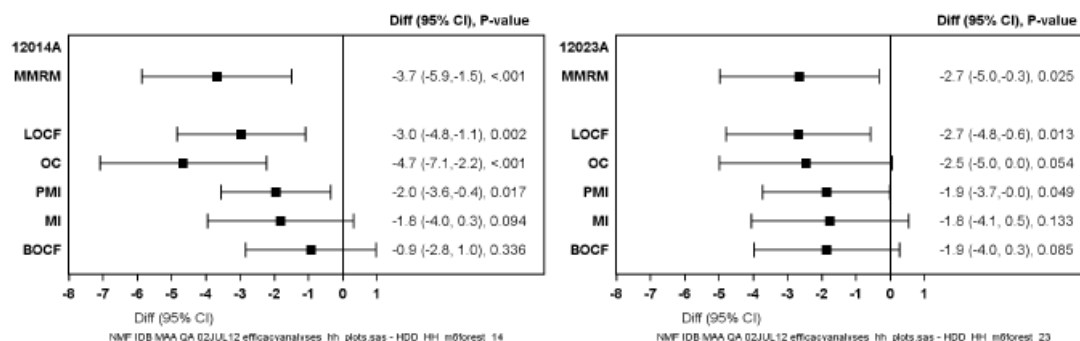
For change from baseline in TAC the ANCOVA, LOCF and PMI analyses were all statistically significantly in favour of nalmefene. In the OC analyses, the difference to placebo was slightly larger than in the primary analysis, but not statistically significant.

Subgroup of patients with *high* or *very high* DRL at baseline and randomisation

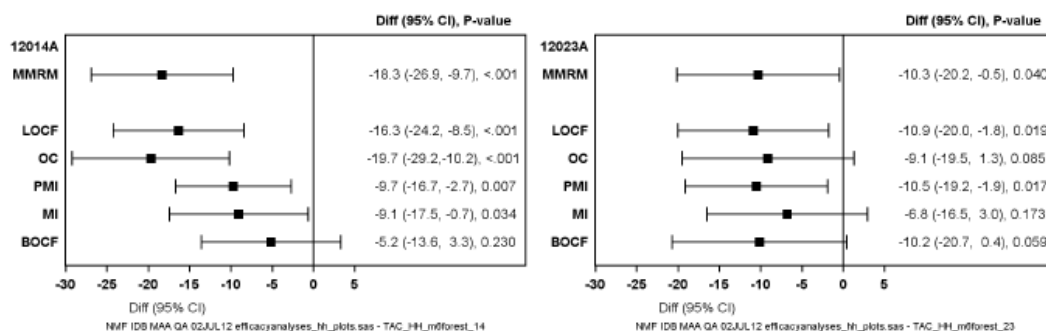
The differences in treatment effect between nalmefene and placebo, and the reduction in alcohol consumption in terms of reduction in HDDs and TAC was inconsistent across the various sensitivity analyses (MMRM, LOCF, OC, PMI, MI and BOCF), and there was a degree of uncertainty regarding the precise magnitude of the beneficial effects (or which analytical method between was best suited to measure it) and its clinical relevance in the total population.

Therefore, *post-hoc* subgroup analyses were performed to substantiate the clinical efficacy and the clinical relevance of nalmefene, and most particularly in order to define a population where the benefit of Selincro would be greatest. The Applicant performed a *post-hoc* subgroup analysis including patients with *high* or *very high* Drinking Risk Level (DRL) at baseline and who maintained a *high* or *very high* DRL at randomisation. A number of analytical methods were used to evaluate the data (MMRM, LOCF, OC, PMI, MI and BOCF). See panels below

Panel 2 Sensitivity Analyses – Changes from Baseline to Month 6 in HDDs (days/month) (FAS) – Patients with a High or Very High DRL at Baseline and Randomisation – Studies 12014A and 12023A



Panel 3 Sensitivity Analyses – Changes from Baseline to Month 6 in TAC (g/day) (FAS) – Patients with a High or Very High DRL at Baseline and Randomisation – Studies 12014A and 12023A



The treatment effect was larger in the patients with a *high* or *very high* DRL at baseline and randomisation than in the total population. At Month 6, the mean difference to placebo (MMRM) was -3.7 HDDs/month and -18.3 g/day in Study 12014A, and -2.7 HDDs/month and -10.3 g/day in Study 12023A.

In addition to the above, to circumvent the complexity of selecting one imputation method over others, a further analysis was carried out, in which all withdrawals were treated as non-responders, looking at results at month 6 for 'completers' (those patients who had maintained a *high* or *very high* DRL at randomisation, continued treatment and completed the study).

In Study 12014A, the proportion of patients who withdrew was higher in the Selincro group than in the placebo group (50% versus 32%, respectively). For HDDs there were 23 days/month at baseline in the Selincro group (n=171) and 23 days/month at baseline in the placebo group (n=167). For the patients who continued in the study and provided efficacy data at Month 6, the number of HDDs was 9 days/month in the Selincro group (n=85) and 14 days/month in the placebo group (n=114). The TAC was 102 g/day at baseline in the Selincro group (n=171) and 99 g/day at baseline in the placebo group (n=167). For the patients who continued in the study and provided efficacy data at Month 6, the TAC was 40 g/day in the Selincro-group (n=85) and 57 g/day in the placebo group (n=114).

In Study 12023A, the proportion of patients who withdrew was slightly higher in the Selincro group than in the placebo group (30% versus 28%, respectively). For HDDs there were 23 days/month at baseline in the Selincro group (n=148) and 22 days/month at baseline in the placebo group (n=155). For the patients who continued in the study and provided efficacy data at Month 6, the number of HDDs was 10 days/month in the Selincro group (n=103) and 12 days/month in the placebo group (n=111). The TAC was 113 g/day at baseline in the Selincro group (n=148) and 108 g/day at baseline in the placebo group (n=155). For the patients who continued in the study and provided efficacy data at Month 6, the TAC was 44 g/day in the Selincro group (n=103) and 52 g/day in the placebo group (n=111).

- Study 12013A (Persistence of efficacy: 52-week)

Supportive evidence of the long-term efficacy of nalmefene in the treatment of AD is based on the results from the 52-week, double-blind, placebo-controlled study (Study 12013A). The double blind comparison of NMF vs placebo lasted over the entire 52 week treatment period, the last 4 weeks of the initial 24 weeks treatment were chosen for calculation of the co-primary efficacy endpoints (change in HDDs and TAC as compared to baseline).

The baseline alcohol consumption of participants in study 12013A (15 HDDs, 75g/day TAC) was slightly below the drinking level observed at baseline for the pooled FAS of studies 12014A and 12023A (19.3 HDDs, 87.7g/day TAC).

A total of 675 patients were randomised (3:1 nalmefene to placebo) to the 52-week treatment period. In the NMF treatment arm slightly fewer patients withdrew (38%) despite the longer treatment duration as compared to withdrawal rates in the NMF treatment arms during the 24-week studies 12014A and 12023A (54% and 43% withdrawal, respectively).

Patient Disposition – Study 12013A

	PBO	NMF	Total
Patients randomised	166	509	675
Patients treated	164 (100%)	501 (100%)	665 (100%)
Patients completed	112 (68%)	310 (62%)	422 (63%)
Patients withdrawn	52 (32%)	191 (38%)	243 (37%)
FAS	137	415	552

In the NMF arm, the IMP was taken on about 48% of treatment days. In about every second of these days (23/48=47.9%) no alcohol was consumed thereafter. However, the portion of abstinence on days with IMP intake was about similar in the placebo arm (23/53=43.4%). Patients appeared to reliably be able to predict days with high drinking liability. In the vast majority of days without IMP intake, no alcohol was drunk both in the NMF (44/51=86.3%) and in the placebo arm (42/47=89.4%).

The high degree of study adherence (92% for NMF, 95% for placebo) as well as the reliability of the patient's self-assessment of drinking propensity on a particular day was supportive for the as-needed treatment regime proposed for nalmefene.

Similarly to the results observed in studies 12014A and 12023A, the difference between NMF and placebo in reducing HDDs and TAC was small over the entire 52 week treatment period, leading to only numerical superiority at some assessment time points (e.g. Month 6, when the primary endpoint was defined) and to statistically significant superiority for both HDDs and TAC at the end of the 52 week treatment period.

The main treatment effect occurred within the first four weeks. Thereafter, the number of HDDs and the total amount of alcohol consumption was nearly maintained or slightly declined. The treatment effect of NMF following the as-needed administration regimen was maintained over the one-year observation period under double blind conditions.

Fifty-two percent of the total 675 patients had a high or very high DRL at baseline. Of these, 52% (representing 27% of the total population) continued to have a high or very high DRL at randomisation. In this post-hoc target population of 183 patients, more patients receiving nalmefene discontinued (63 [45%]) as compared to those receiving placebo (13 [31%]). For HDDs there were 19 days/month at baseline in the Selincro-group (n=141) and 19 days/month at baseline in the placebo group (n=42). For the patients who continued in the study and provided efficacy data at 1 year, the number of HDDs was 5 days/month in the Selincro group (n=78) and 10 days/month in the placebo group (n= 29). The TAC was 100 g/day at baseline in the Selincro group (n=141) and 101 g/day at baseline in the placebo group (n=42). For the patients who continued in the study and provided efficacy data at 1 year, the TAC was 24 g/day in the Selincro group (n=78) and 47 g/day in the placebo group (n=29).

Summary of main efficacy results

Efficacy results were obtained from two pivotal trials (study 12014A: n=579, study 12023A: n=655) following identical study designs, covering different regions across Europe. The severity level of AD of included subjects was rather low (ADS score 13.6).

Table 2. Summary of key efficacy results for the two pivotal studies 12014A 12023A

	Results and Analysis				
Analysis description	Primary Analysis				
Analysis population and time point description	1. All-patients-randomised set (APRS) – all randomised patients. 2. All-patients-treated set (APTS) – all patients in the APRS excluding those with no recorded IMP intake and all IMP returned. 3. Full-analysis set (FAS) – all patients in the APTS who had at least one valid post-baseline assessment. Week 24 primary efficacy time point				
Descriptive statistics and estimate variability	Treatment group	Study 12014A nalmefene	Study 12014A Placebo	Study 12023A nalmefene	Study 12023A placebo
	Number of subjects (FAS)	290	289	329	326
	Co-primary endpoint Mean change from baseline in HDDS ± SE (days per month) (MMRM analysis)	n=152 -11.2 ± 0.6	n=213 -8.9 ± 0.6	n=212 -12.3 ± 0.5	n=229 -10.6 ± 0.5
	Mean difference to placebo ± SE (95% CI) p-value	-2.3 ± 0.8 (-3.8; -0.8) p=0.002		-1.7 ± 0.7 (-3.1; -0.4) p=0.012	
	Co-primary endpoint Mean change from baseline TAC ± SE (g/day) (MMRM analysis)	n=152 -50.7 ± 2.4	n=213 -39.7 ± 2.2	n=212 -59.0 ± 2.3	n=229 -54.1 ± 2.2
	Mean difference to placebo ± SE (95% CI) p-value	-11 ± 3.0 (-16.8; -5.1) p<0.001		-5.0 ± 2.9 (-10.6; 0.7) p=0.088	
	Key secondary endpoint RSDRL %responders	n=290 37%	n=289 44%	n=329 68%	n=326 67%
	Odds ratio for response (95% CI) p-value	0.70 (0.50; 0.98) p=0.03 Non-response imputation		1.28 (0.89; 1.83) p=0.183 TAC-derived MMRM	
	CGI-S and CGI-I Adjusted change from baseline I to week 24	n=152	n=210	n=203	n=225
	CGI-S Mean difference to placebo ± SE (95% CI) p-value	-0.4 ± 0.1 (-0.6; -0.2) p<0.001		-0.2 ± 0.1 (-0.44; -0.02) p=0.029	
	CGI-I Mean difference to placebo ± SE (95% CI) p-value	-0.3 ± 0.1 (-0.5; -0.02) p<0.001		-0.2 ± 0.1 (-0.38; 0.04) p=0.111	
	% CDT	n=152	n=207	n=195	n=216
	Mean difference to placebo ± SE (95% CI) p-value	-0.1 ± 0.1 (-0.3; 0.1) p=0.291		0.1 ± 0.1 (-0.2; 0.3) p=0.559	
	GGT Adjusted geometric mean at week 24	n=158 40.3	n=211 45.7	n=207 43.4	n=224 45.0
	Ratio to placebo (95% CI) p-value	0.88 (0.80; 0.97) p=0.009		0.96 (0.86; 1.08) p=0.529	

Analysis performed across trials (pooled analyses and meta-analysis)

Key Secondary Efficacy Analysis – RSDRL

RSDRL response was defined as a downward shift from baseline in DRL:

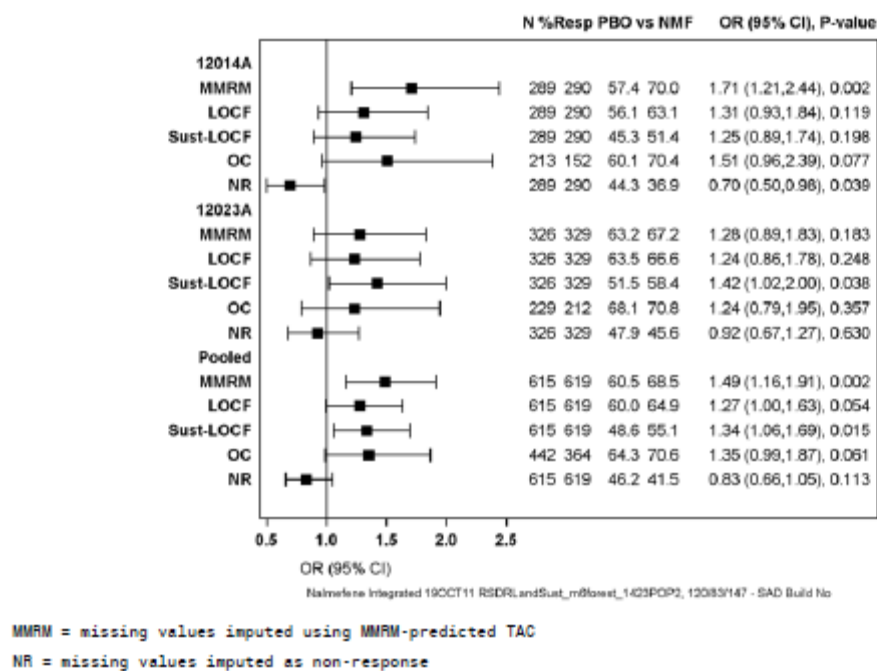
- for patients with a *very high* DRL at baseline: a shift to *medium* DRL or below
- for patients with a *high* or *medium* DRL at baseline: a shift to low DRL

The key secondary efficacy analysis was performed on the pooled data from Studies 12014A, 12023A, and 12013A, as pre-specified prior to unblinding any of the studies, as well as on the pooled data from Studies 12014A and 12023A, as pre-specified prior to unblinding Study 12023A. The pooled data from Studies 12014A and 12023A, are considered here first.

In the analysis of RSDRL using pooled data from Studies 12014A and 12023A, the odds ratio (OR) for response was in favour of nalmefene (OR = 1.49, $p < 0.01$) when missing values were imputed using MMRM-predicted TAC values (Panel 79).

The results of the responder analyses using different imputation methods were in favour of nalmefene, with the exception of the analysis that imputed missing values as non-response [NR] (see panel below).

Panel 79 Key Secondary Analysis (RSDRL) – Proportion of Responders (%) and Odds Ratio for Response at Month 6 (FAS, LREG) – Studies 12014A, 12023A, and Studies 12014A and 12023A Pooled



However, for the majority of the patients who withdrew, their alcohol consumption was stable (or decreasing) up to the time of withdrawal.

In the analysis of RSDRL in the patients with a *high* or *very high* DRL at baseline (pooled data from Studies 12014A and 12023A), the results were similar to those in the corresponding total population.

In the analysis of RSDRL using pooled data from Studies 12014A, 12023A, and 12013A, the results were consistent with those using pooled data from Studies 12014A and 12023A (data not shown in detail here).

RSDRL analyses show that for the pooled data significant differences for nalmefene compared to placebo were observed. Pooling of data was pre-specified. The results of the pooled 12014A and 12023A dataset as show above are considered the most relevant. The responder analyses also rely on MMRM predicted TAC estimates therefore considerations on missing data apply. MMRM results show the response from the perspective of efficacy for patients adhering to treatment. The set of sensitivity analyses allows concluding that a statistically significant difference was demonstrated, as they are regarded as conservative response estimates.

2.5.2. Supportive studies

The Applicant provided further analyses on the expected harm reduction (alcohol-related physical health outcomes, injuries or social consequences) based on literature data as well as modelling from the clinical trial data to support the clinical benefit of the observed effect.

Alcohol Consumption Modelling Report

An Alcohol Consumption Modelling Report was provided modelling the consequences of heavy drinking days and total alcohol consumption in terms of alcohol-attributable diseases and injuries. Alcohol consumption was simulated, day by day, at patient level for 12 months, using statistical equations estimated from nalmefene clinical trial data. The statistical methods used for simulation are acceptable. Individual patient data for HDDs and TAC were simulated. Model selection for odds of drinking and count data for alcohol consumption was based more on empirical considerations than on theoretical assumptions, and was considered acceptable. The model was used to generate a dataset of 200.000 untreated alcohol dependent patients. Using this dataset, it was possible to translate alcohol reduction into harm reduction by modelling the consequences of alcohol reduction in terms of health and social events, thus comparing probabilities of events between different groups of patients (according to the number of HDDs and TAC over 12 months).

The number of HDDs over 1 year was divided into 8 categories with a range of 20 HDDs over a year, in order to represent a difference of 2 monthly HDDs vs placebo. For all diseases or injuries, the number of events increases with the number of HDDs per year both for male and female.

Panel 15 Number of Events per 100 000 Patient-Years by Category of Number of HDDs (Males and Females)

HDD range (days)	Ischemic Heart Disease	Ischemic Stroke	Traffic Injuries	Other Injuries	Cirrhosis	Pancreatitis	Pneumonia	Haemorrhagic stroke
<100	1563	494	303	2434	330	141	1827	149
100-120	1707	538	398	3085	428	188	1957	171
120-140	1819	572	465	3602	505	235	2046	188
140-160	1928	606	531	4112	582	291	2120	203
160-180	2027	637	598	4553	686	391	2217	223
180-200	2118	666	668	4953	836	596	2340	248
200-220	2211	695	747	5361	1084	1136	2523	284
>220	2300	724	822	5742	1378	2251	2705	323

HDD: Heavy drinking days

The TAC per year was divided into 14 categories with a range of 3000g over a year, in order to represent the difference of a monthly average of 10g per day vs placebo.

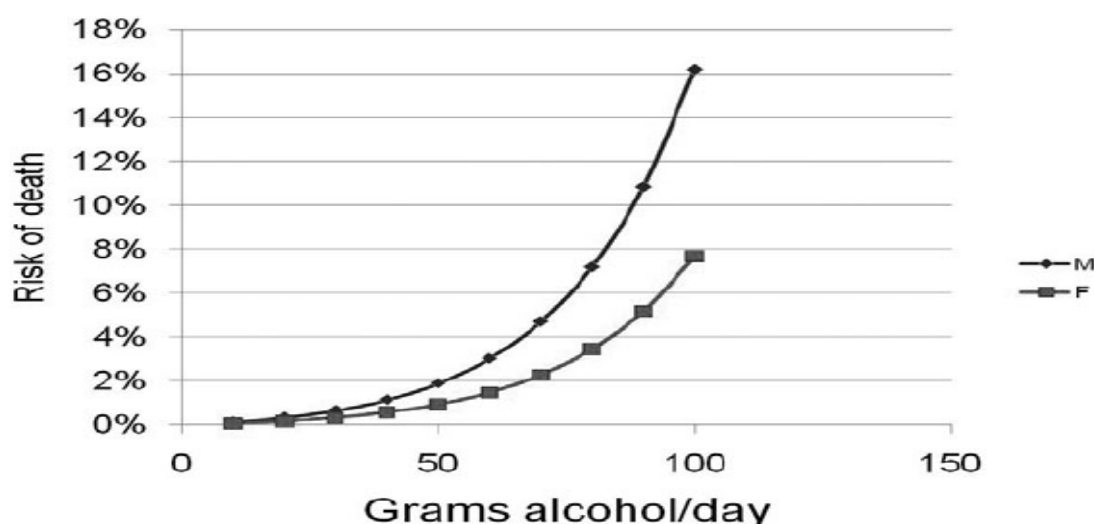
Panel 19 Number of Events per 100 000 Patient-Years by TAC Category (Males and Females)

TAC Range (g)	Ischemic Heart Disease	Ischemic Stroke	Traffic Injuries	Other Injuries	Cirrhosis	Pancreatitis	Pneumonia	Haemorrhagic stroke
<15000	1465	467	239	2034	269	116	1731	134
15000-18000	1562	498	304	2492	322	132	1812	149
18000-21000	1640	524	358	2881	370	150	1879	161
21000-24000	1721	551	412	3278	424	175	1950	174
24000-27000	1810	579	467	3691	483	206	2022	189
27000-30000	1895	605	519	4071	548	248	2095	204
30000-33000	1964	626	568	4383	621	303	2173	221
33000-36000	2024	645	613	4652	703	380	2254	239
36000-39000	2076	661	655	4887	794	485	2340	259
39000-42000	2122	675	693	5089	899	636	2435	280
42000-45000	2157	686	726	5248	1017	866	2528	303
≥45000	2216	704	773	5508	1234	1435	2691	336

TAC: Total alcohol consumption

The modelling data represent the net treatment effect of nalmefene over placebo and point to a clinically relevant reduction of alcohol-associated events like transport injuries, ischemic heart disease, pancreatitis etc. if alcohol consumption is reduced to the degree that was achieved with nalmefene in the chosen patient collective. The model showed that even a moderate decrease in drinking levels might be associated with a decrease in both harmful events (e.g. mortality rates; accidents, see figure below) and a decrease in relative risk of the medical issues typically linked to excessive alcohol drinking (e.g. liver cirrhosis).

Alcohol Consumption Has an Exponential Relationship to Harmful Events –Risk of Death



Furthermore, systematic literature review data on alcohol-related physical health outcomes were provided. A significant reduction of mortality was calculated by correlating the net drinking amount reduction over placebo with epidemiological data.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of nalmefene in the Treatment of alcohol dependence with an as needed dose of nalmefene 18 mg was evaluated in three randomised, double-blind, placebo-controlled studies: two 6-month studies (Studies 12014A and 12023A) and one 1-year study (Study 12013A). In all three studies, the patient population consisted of patients with a diagnosis of alcohol dependence according to the DSM-IV-TR™ criteria.

All participants received a psychosocial support to aid compliance called BRENDA. Efficacy was evaluated over 24 weeks in both pivotal studies with a 4 week run-out period. The duration is reasonable for establishing a clinically significant reduction in alcohol consumption. Long-term efficacy was evaluated as a secondary objective of a one-year safety and tolerability study.

The applicant designed their studies with harm reduction as a consequence of reduced alcohol as the main goal of treatment rather than as an intermediate step on the way to full abstinence.

The number of Heavy Drinking Days (HDDs, defined as a day with alcohol consumption ≥ 60 g for men and ≥ 40 g for women) and Total alcohol consumption (TAC, defined as mean daily alcohol consumption in g/day over 28 days) were defined as co-primary endpoints. Among numerous other secondary endpoints, responder analyses in terms of downward shift of DRL and 30/50/70%-reductions of TAC were performed.

The design of the Applicant's pivotal studies was acceptable and in line with current guideline provisions.

Efficacy results

In the total study population, the number of HDDs was reduced from 19.3 per month at baseline by -11-12 per month with a net difference over placebo of -2.3 (p 0.002, study 12014A) and -1.7 (p 0.012, study 12023A) HDDs per month (MMRM). TAC (87.7g per day at baseline) was reduced by 50-60 g per day after 24 weeks with a net difference over placebo of -11.0 g/day (p<.001, study 12014A) and -4.9 g/day (p 0.088, study 12023A). In summary:

In study 12014A: **HDDs** [MMRM, Diff (95%CI)]: -2.3 (-3.8,-0.9; p 0.002)

TAC [MMRM, Diff (95%CI)]: -11.0 g (-16.8, -5.1; p<0.001).

In study 12023A: **HDDs** [MMRM, Diff (95%CI)]: -1.7 (-3.1,-0.4; p 0.012)

TAC [MMRM, Diff (95%CI)]: -4.9 g (-10.6, 0.7; p 0.088).

These differences in treatment effect between nalmefene and placebo were considered by the CHMP small, not consistently statistically significant across co-primary endpoints, and with a degree of uncertainty with regards to clinical relevance in the total population.

Interpretation of these efficacy results observed for the FAS was complicated by the fact that a considerable number of subjects (18% in study 12014A, 33% in study 12023A) almost entirely finished drinking during the 1-2 week time period between screening and randomisation. In these pre-random-reducers there was virtually no space for further improvement either by BRENDA interventions or IMP intake.

Analysis of the efficacy results was further complicated by the issue of study discontinuation in both pivotal trials: high levels of patient withdrawal were seen across both pivotal studies. The proportion of patients who withdrew was high in the Alcohol Dependence Pool (33.9% in the placebo group and 42.9% in the nalmefene group). Withdrawal of consent was the primary reason for withdrawal for 13.3% of the patients in the placebo group and for 15.7% of the patients in the nalmefene group and was the most common primary reason in both treatment groups. The high withdrawal rate renders imputation of missing data an important issue when determining statistical significance of primary efficacy endpoints.

To resolve the issues above, and in order to define a population where the benefit of Selincro would be greatest, the Applicant proposed to focus the target population of nalmefene on those patients with *high* or *very high* drinking risk level at baseline and randomisation. Therefore, they performed a post-hoc subgroup analysis including patients with *high* or *very high* Drinking Risk Level (DRL) at baseline and who maintained a high or very high DRL at randomisation.

- In study 12014A, 78.2% of patients had a high or very high DRL at baseline; of these, 75% (representing 58% of the total study population) continued to have a high or very high DRL at randomisation.

- In study 12023A, 77.5% of patients had a high or very high DRL at baseline; of these, 59% (representing 46% of the total study population) continued to have a high or very high DRL at randomisation.

In this subgroup of *high* or *very high* DRL at baseline and randomisation, the number of HDDs was reduced from 22.6 per month at baseline to 10-11 per month after 24 weeks with a net difference over placebo of -3.7 (p 0.001, study 12014A) and -2.7 (p 0.025, study 12023A) HDDs per month (MMRM). TAC was reduced with a net difference over placebo of -18.3 g/day (p<0.001) in study 12014A and -10.3 g/day (p 0.04) in study 12023A, after 24 weeks. In summary:

In study 12014A: **HDDs** [MMRM, Diff (95%CI)]: -3.7 (-5.9, -1.5; p<0.001)
 TAC [MMRM, Diff (95%CI)]: -18.3 (-26.9, -9.7; p<0.001).

In study 12023A: **HDDs** [MMRM, Diff (95%CI)]: -2.7 (-5.0, -0.3; p 0.025)
 TAC [MMRM, Diff (95%CI)]: -10.3 (-20.2, -0.5; p 0.040).

As outlined above, the net treatment effect over placebo in terms of HDD/TAC reduction and associated responder analyses was generally more pronounced in the subgroup of patients with *high* or *very high* DRL at baseline and randomisation as compared to the total population. The results of the secondary responder analyses (two-category downward shift in DRL, shift to low DRL, 70% reduction in TAC) supported those of the co-primary endpoints.

However, the CHMP considered that the magnitude of the beneficial effects was still inconsistent (varying depending on which analytical method between MMRM, LOCF, OC, PMI, MI or BOCF was used to measure it) and that its clinical relevance had not been fully elucidated. Therefore, questions were addressed to the Bio-Statistic Working Party (BSWP) on the appropriateness of the different sensitivity analyses and to the Psychiatry SAG Committee on the clinical relevance of the treatment effect achieved with nalmefene, as summarised below.

Additional expert consultation

To contribute to the elucidation of the above uncertainties, the Bio-Statistic Working Party (BSWP) was asked for its “view on the validity of the different analyses to provide a reliable estimate of the effect of treatment compared to placebo and baseline and the statistical evidence for the primary endpoints in the pivotal studies”.

Additionally, a request was sent to the psychiatry SAG to comment on the clinical relevance of the observed effect. The SAG expertise was also sought on the validity of the choice of reduction in alcohol consumption rather than total abstinence as a therapeutic goal. Finally, the SAG was asked to comment on the appropriateness of having defined a subgroup of patients that is more likely to benefit from nalmefene treatment as target population (i.e. patients with a high or very high DRL at baseline and randomisation) by means of a post-hoc analysis of the data.

The contribution of each additional expert consultation is individually dealt with below.

Bio-Statistic Working Party (BSWP)

In view of the CHMP requests outlined above, the Bio-Statistic Working Party (BSWP) was asked to address the following:

Reduction of alcohol consumption was measured in the pivotal studies 12014A and 12023A with co-primary endpoints as change from baseline in monthly number of Heavy Drinking Days and monthly Total Alcohol Consumption. The applicant proposed to focus on a target population of those patients with baseline high or very high drinking levels who were not reducing their alcohol consumption before randomisation. The treatment effect in this subgroup was more pronounced than in the ITT population. Because a considerable number of missing values due to drop-outs was expected and observed, a number of sensitivity analyses were pre-specified for the ITT population and also performed in the subpopulation. The validity of the different analyses (MMRM as primary analysis, LOCF, OC, Placebo Mean Imputation, Placebo Multiple Imputation and BOCF as sensitivity analyses) to provide a reliable estimate of the effect of treatment compared to placebo and baseline and the statistical evidence for the primary endpoints in the pivotal studies was questioned.

The BSWP provided a response document to the points raised by the CHMP, in which the advantages and disadvantages of each of the methodological analyses were discussed. The report explained that it is not possible to single out one of the six suggested methods as uniformly best. For the subgroup of patients with high or very high DRL at baseline and randomization the MI analysis would suggest an estimated treatment effect of a reduction of about 2 heavy drinking days per month. It is for clinical experts to establish whether even these estimates could be considered to be of clinical relevance.

The fact, however, that 48% of subjects withdrew from treatment in the nalmefene group before the end of the study in study 12014A shows the lack of robust evidence of efficacy at 6 months for all randomised patients.

In the absence of an unequivocally preferred option (due to unverifiable assumptions) the assessment should still consider the pre-specified primary analyses but judge them in the light of the plausibility of the underlying assumption taking the lack of robustness due to the high and differential dropout rate into account. Analyses that had not been presented were:

1. A comparison of responders; with a defined cut-off point of clinical relevance (x) for the number of HDD per month. For example,
 - a. patients with a decrease of $\geq x$ HDD/month for any month in the follow-up period or

- b. patients who completed 6-months of treatment with decrease of $\geq x$ HDD/month in Month 6
2. A 'pattern-mixture' model (which can be constructed making other statistical assumptions on the unobserved data as MMRM and MI above)."

In the light of the above, the Applicant was requested to make a presentation of a newly calculated "pattern-mixture model", constructed making other statistical assumptions on the unobserved data than the mixed model repeated measures MMRM and placebo multiple imputation MI, in the hope that this may help to further elucidate the effect size estimation.

SAG

In addition to the above, the CHMP requested to convene a Scientific Advisory Group (SAG), to address the questions on the clinical relevance of the observed treatment effect, the treatment goal (in particular, whether the proposed reduction in alcohol consumption rather than achievement of abstinence and/or reduction in frequency and severity of relapse was a valid and desirable treatment goal of pharmacological intervention in alcohol-dependent patients and, if so, whether the primary care setting would be appropriate) and the target population (i.e. those patients with a *high* or *very high* DRL at baseline and who had maintained it at randomisation).

The key outcome of the Psychiatry SAG Meeting is summarized hereof. The Group noted the model presented by the Applicant showing that even a moderate decrease in drinking levels might be associated with a decrease in both harmful events (e.g. mortality rates; accidents) and a decrease in relative risk of the medical issues typically linked to excessive alcohol drinking (e.g. liver cirrhosis). The SAG confirmed that, however modest, the effect size of NMF was clinically meaningful. Additionally, the SAG recognised the validity of the post-hoc analysis defining the target population. Whilst it was acknowledged that post-hoc analyses are not ideal, it was stated that they are commonly used in clinical trials for psychiatric drugs, given the high dropout rates encountered in these populations. The SAG also acknowledged that the reduction in alcohol consumption is an appropriate goal in a subgroup of alcohol dependent patients with *high* or *very high* drinking risk level (HDRL, VHDRL) without physiological signs of withdrawal and not requiring any immediate detoxification procedure. To avoid misleading clinicians and to minimise off-label use, the group emphasized that the therapeutic indications should clearly instruct physicians (including general practitioners) to easily recognise the patients who could be the target of the drug.

The SAG also confirmed that the study population is representative of the population for whom nalmefene is proposed to be prescribed. Based on the data provided, HDRL/VHDRL patients are more likely to be the target population who could benefit from nalmefene treatment.

The first recommendation of the BSWP, definition of a clear cut-off point of clinical relevance (x) for the number of HDD per month, was not formally addressed by SAG experts. However, the experts confirmed that the effect size of nalmefene shown in pivotal trials, albeit modest, was clinically relevant.

Further to the above outcomes and requests of the BSWP and SAG, the Applicant made a presentation to the CHMP, largely focussed on statistical content. They presented on the therapeutic effect by illustrating it via the statistical models requested. In particular, an analysis was presented based on the "pattern mixture model" PMM selected by the BSWP to evaluate the impact of deviations from the underlying assumption behind the MMRM. By introducing different deltas, different patterns of alcohol consumption for withdrawn patients were explored.

The conclusions from the applicant presentation were that both responder analyses based on the number of heavy drinking days (HDDs) at Month 6 confirmed the efficacy of nalmefene and were consistent with the results of the responder analyses based on total alcohol consumption (TAC).

The PMM results based on the assumption of $\Delta = 2$ for HDDs and $\Delta = 10$ for TAC were considered by the Applicant unlikely to be biased in favour of nalmefene, with an estimated treatment effect compared to placebo of -2.7 (-4.8; -0.6); $p=0.013$ [Study 12014A] and -2.5 (-4.8; -0.1); $p=0.040$ [Study 12023A] for HDDs and of -13.7 (-22.1; -5.2); $p=0.001$ [Study 12014A] and -9.3 (-19.4; 0.7); $p=0.069$ [Study 12023A] for TAC (g/day), i.e. approximately 2.5 HDDs/month and 10g/day in both 6-month efficacy studies.

Based on the above effect size, the applicant explained why in their view the observed effect was clinically relevant, using direct and indirect evidence, addressing various CHMP questions and the specific statistical methodology questions raised by the BSWP.

In particular, as the BSWP had expressed interest in the treatment effect at the end of the 6 month treatment period, the applicant focused on month 6 (end of treatment period) with regards to the responder analyses. Clarifications were provided on the primary method of imputation based on the MMRM. Based on the available data from the Applicant's studies, for withdrawn patients, the alcohol consumption was stable up to time of withdrawal, and alcohol consumption after the last dose of IMP did not increase.

After the Oral Explanation the CHMP discussed the possible relevance of clinical effect of a reduction that was quantified as approximately 2 heavy drinking days (HDD) per month. The SAG view on the fact that, however modest, the effect size of nalmefene was to be considered clinically meaningful was noted. Concern was expressed on the possible occurrence of withdrawal symptoms and how to identify those patients with withdrawal symptoms in order to exclude them from taking Selincro. The CHMP recommended that the product information for Selincro would not include reference to any assumptions, but only responders' analysis with withdrawals imputed as failures (non-responders).

2.5.4. Conclusions on the clinical efficacy

Overall effect size

In the adjusted target population as defined above (patients with *high* or *very high* DRL at baseline and who maintained a *high* or *very high* DRL at randomisation) a more than 50% reduction of drinking amounts in terms of HDD and TAC was achieved by the combined use of as-needed active treatment administration and accompanying BRENDA interventions. The mean number of heavy drinking days (HDDs) decreased from 23 days/month at baseline to 11 days/month at Month 6 in Study 12014A and from 23 days/month to 10 days/month in Study 12023A. The mean TAC decreased from 102 g/day at baseline to 44 g/day at Month 6 in Study 12014A, and from 113 g/day to 43 g/day in Study 12023A. This reduction corresponds to approximately 160 additional days per year with no heavy drinking and to the equivalent of 330 fewer bottles of wine consumed per year.

Robustness of the net effect over placebo

In the primary analysis (based on MMRM), the difference in the reduction of alcohol consumption between nalmefene and placebo ranged from 2.7 HDDs/month to 3.7 HDDs/month and from approximately 10g/day to approximately 18g/day. This translates into approximately 1½ months fewer HDDs per year and almost 80 bottles of wine fewer per year with nalmefene compared to placebo.

The proportion of patients who withdrew in the Applicant-sponsored studies was comparable to that in other placebo-controlled clinical studies conducted in patients with AD over the last 10 years (e.g. Combine study 2006, Anton et al.). In Study 12014A, the proportion of patients who withdrew was higher in the nalmefene group than in the placebo group (NMF 48%, PBO 26%). In the identical second 6-month study, Study 12023A, the proportion of patients who withdrew was similar in both treatment groups (NMF 36%, PBO 30%). Various sensitivity analyses were performed to evaluate how different assumptions would influence the estimates of the treatment effect versus placebo.

All the sensitivity analyses were in favour of nalmefene, irrespective of the imputation method.

The CHMP recommended the following wording for SmPC section 4.1 as the one that would most accurately reflect the pivotal trial data and specify the target population and prescribing conditions most appropriate for nalmefene treatment:

Selincro is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (see section 5.1), without physical withdrawal symptoms and who do not require immediate detoxification.

Selincro should only be prescribed in conjunction with continuous psychosocial support focussed on treatment adherence and reducing alcohol consumption.

Selincro should be initiated only in patients who continue to have a high drinking risk level two weeks after initial assessment.

This indication wording needs to be seen in conjunction with the wording in section 4.2, in particular with regards to monitoring instructions and duration of treatment.

Section 5.1 of the SmPC has also carefully been worded in order to accurately reflect clinical data in the efficacy pivotal trials. No reference to assumptions is made, but only the responders' analysis with withdrawals imputed as failures (non-responders) has been included. Results at month 6 are stated for 'completers' (those patients who had maintained a *high* or *very high* DRL at randomisation, continued treatment and completed the study).

2.6. Clinical safety

Due to almost identical design and patient inclusion criteria, the three Lundbeck studies 12014A, 12023A and 12013A were summarized as the Alcohol Dependence Pool.

The Alcohol-use Disorders Pool comprises the patients from the placebo and NMF groups of the five phase II/III studies CPH-101-0801, CPH-101-0701, CPH-101-0299, CPH-101-0399, and CPH-101-0400, conducted by the former licensee Biotie.

Patient exposure

The All-patients-being-treated Set (APTS) in the Alcohol Dependence Pool comprised 1941 patients who either had recorded IMP intake or did not return all their IMP: 797 in the placebo group and 1144 in the nalmefene group.

In the Alcohol-use Disorders Pool a total of 361 patients in the placebo group and 689 patients in the nalmefene groups were included.

Overall, in the Alcohol Dependence Pool the IMP was taken on 62.1% of days in the placebo group, and on 50.8% of days in the NMF group.

Withdrawal

The proportion of patients who withdrew was high in the Alcohol Dependence Pool (33.9% in the placebo group and 42.9% in the nalmefene group). Withdrawal of consent was the primary reason for withdrawal for 13.3% of the patients in the placebo group and for 15.7% of the patients in the nalmefene group and was the most common primary reason in both treatment groups. For 3.8% of the patients in the placebo group and 10.5% of the patients in the nalmefene group, the primary reason for withdrawal was adverse events.

Adverse events

TEAEs (Alcohol Dependence Pool)

The incidence of TEAEs was rather high both for placebo (in 500/797=62.7% of patients) and for nalmefene (in 855/1144=74.7% of patients). Unspecific TEAEs like dizziness, nausea, headache and insomnia prevail. Dizziness, nausea and insomnia/sleep disorders occurred about 3-4 times more often in subjects receiving NMF.

More than ten percent of subjects receiving nalmefene experienced severe related TEAEs like dizziness, nausea, insomnia, or vomiting.

The incidence of TEAEs was not dependent upon the Drinking Risk Level at baseline. TEAEs occurred in 74.7% of NMF patients (placebo 62.7%) of the entire Alcohol Dependence Pool, 74.8% of NMF patients (placebo 62.3%) with high or very high DRL and 75.8% of NMF patients (placebo 64.4%) with medium DRL.

Comparison of pools

The most frequently observed TEAEs of nalmefene are very similar for the Alcohol Dependence Pool and the Alcohol-use Disorder Pool. In the Alcohol-use Disorder Pool, subjects were included that received different nalmefene doses (5, 10, 20, 40 mg). However, there was no clear dose-relationship in the types or incidences of adverse events among dose groups.

Onset and duration of TEAEs leading to withdrawal

TEAEs leading to withdrawal in the Alcohol Dependence Pool occurred much earlier in subjects receiving NMF (median 7 days) than in subjects receiving placebo (median 63 days). After onset, TEAEs leading to withdrawal lasted considerably shorter in the NMF group (5 days) as compared to placebo (47 days), until the decision for withdrawal due to AE was taken.

Time course of frequent TEAEs

The frequent TEAEs nausea [dizziness] mostly occurred within the first month of treatment with an incidence of 18.1% [15.7%]. Thereafter the incidence decreases dramatically to about 1-2% per month. Despite the short median duration of nausea and dizziness (3 days each) it appears to prevail for considerable time in some patients, since the rate of ongoing nausea / dizziness outnumbers the incidence rates from month 2-13.

Insomnia / sleep-related events

The overall incidence of insomnia was 5.4% in the placebo group and 13% in the nalmefene group. A total of 0.3% of the patients in the placebo group and 0.9% of the patients in the nalmefene group had insomnia that led to withdrawal.

Sleep-related events (insomnia, somnolence, nightmares, fatigue, etc.) were frequently observed with 29.3% of subjects receiving nalmefene reporting either night- or day-time events. In overall 4.9% of subjects symptoms occurred both at night- and day-time. Insomnia is listed as a very commonly occurring AE and sleep disorders as a commonly adverse event in section 4.8 of the proposed SmPC.

Hepatic function disorders

Hepatic disorders, either potentially drug-related or specifically reported as alcohol-related, occurred at similar frequencies in the nalmefene and the placebo group. There were four cases of alcoholic liver disease in the nalmefene group and none in the placebo group. Overall, the differentiation between potentially drug-related and specifically alcohol-related hepatic disorders is difficult to make. It is concluded that nalmefene does not additionally compromise hepatic function. Increases in liver enzymes like ALAT, AST and GGT were similar in both groups. The incidences of other potential indicators of liver function disorders, like INR increased, prolonged prothrombin time or hypoalbuminaemia were < 0.2% for nalmefene.

Selected psychiatric events

Psychiatric disorders such as confusion, abnormal thinking, and hallucination occurred in 2.9% of subjects receiving nalmefene, i.e. about three times more often than in the placebo group. In seven cases, confusion / delusion / hallucination was rated as severe. In studies included in the Alcohol Dependence Pool subjects with existing psychiatric co-morbidities were not included. Confusional state and hallucination are listed as psychiatric disorders in section 4.8 of the proposed SmPC.

AEs potentially related to suicidality

Two patients in the placebo group committed suicide.

In the nalmefene group, there were two cases of self harm / suicidal behaviour after long-standing regular nalmefene intake. The majority of adverse events potentially related to suicidality (7/9) regard cases of intentional overdose, not necessarily with suicidal intention, but in an attempt to increase efficacy. In the majority of these cases, two tablets were taken.

Latent suicidality of the patient has to be borne in mind by the treating physician when dealing with alcohol dependent patients. Overall, it is concluded that in the available clinical trial database (incl. Alcohol Dependence Pool and Alcohol-use Disorder Pool) there was no signal for nalmefene pointing to increased suicidality of the patients.

Adverse events of special interest (others)

Depressive symptoms (encompassing depressed mood, anhedonia, dysphoria, depression etc.) were reported in 37/1144 patients in the nalmefene group (3.2%) and 22/797 patients in the placebo group (2.8%).

Based on the available database, nalmefene does not appear to raise the incidence of accidents and falls in the target population of alcohol dependent patients.

Convulsions (SMQ), encompassing alcohol seizure, convulsion and epilepsy, occurred in only 5 out of 1144 patients receiving nalmefene (0.4%) [placebo group: 4 out of 797 patients (0.5%)]. At least in three of the five cases a causal relationship with nalmefene is unlikely, since convulsions occurred more than three weeks after the most recent dose.

In the clinical trials, nalmefene was not liable to drug abuse or dependence.

Role of alcohol intake on TEAE occurrence

The overall rate of patients with TEAEs within 1 day after first dose of IMP was 40.0% in NMF patients without alcohol and 41.3% in NMF patients with alcohol intake. Apart from similarity of the overall incidence rate of TEAEs there was also no striking difference for single AEs of particular interest (NMF group TEAE rate without / with alcohol: nausea 12.7 vs 15.1%, fatigue 4.2 vs 5.1%, dizziness 14.8 vs 13.5%, headache 5.5 vs 5.1%, abnormal dreams 0.3 vs 0.4%, anxiety 1.8 vs 1.6%, insomnia 5.8 vs 6.2%, hyperhidrosis 4.5 vs 2.4%).

It therefore appears that TEAEs were mostly related to the intake of nalmefene itself, rather than the combination of nalmefene with alcohol. The feeling of malaise which deters the patients from drinking occurs for disulfiram only when alcohol is actually consumed. Nalmefene may deter patients from drinking by causing unspecific symptoms like nausea, dizziness etc. before alcohol is actually taken.

2.6.1. Discussion on clinical safety

The incidence of TEAEs was high after nalmefene administration (74.7%). Additionally, study discontinuation due to intolerable AEs was high (10.5%), and may still be underestimated since for a number of patients discontinuing for consent withdrawal, the occurrence of AEs may play a contributory role. TEAEs mainly occurred early at treatment initiation. In the further course of treatment tolerability improves. Mostly, TEAEs were rather unspecific like nausea or dizziness. Notably, many patients reported sleep-related events (either at day- or night-time).

Nalmefene did not appear to additionally compromise hepatic function on top of alcohol-related liver enzyme increases.

A study investigating the pharmacokinetic properties of nalmefene in subjects with renal impairment (mild, moderate, or severe) and in healthy subjects will be carried out as part of the pharmacovigilance activities.

Occurrence of TEAEs was mostly related to the intake of nalmefene itself, rather than the combination of nalmefene with alcohol. However, nalmefene may also deter patients from drinking by causing unspecific symptoms like nausea, dizziness etc. before alcohol is actually taken.

From the safety database, all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics, which also includes warnings on use in patients with concomitant psychiatric comorbidities such as major depressive disorder.

2.6.2. Conclusions on the clinical safety

Overall, there were no serious adverse events causing major safety concern.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the Lundbeck system of pharmacovigilance (Version 12.0 dated June 2012). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provided adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The Applicant submitted an EU Risk Management Plan (EU-RMP) "RMP-EU-2012" – Version 1.0. The Data Lock Point of the EU-RMP was 1 May, 2012. According to Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use – an EU-RMP should be submitted with the application for a new active substance as well as for a new dosage form, new route of administration and significantly differing therapeutic indication of a known active substance. Nalmefene has been marketed outside the EU (e.g. USA, Canada, China, and Mexico) as solution for injection only, in the treatment of opioid overdose and reversal of opioid drug effects. No oral dosage forms have been approved worldwide. Therefore, an EU-RMP is mandatory.

Safety Specification

The important identified risks, important potential risks and important missing information as outlined in the Safety Specification Summary of the submitted EU-RMP are listed in the following table.

Important Identified Risks	Confusional state; hallucination, dissociation Concurrent use with opioids
Important Potential Risks	Off-label use
Important Missing Information	Use in pregnant and lactating women Use in children Genetic polymorphism Use in other ethnic groups than Caucasian Overdose Use in patients with increased (>3 ULN) ALAT or ASAT Use in patients with history of seizure disorder, including alcohol withdrawal seizures Use in elderly Use in patients with significant psychiatric comorbidity Use in patients with significant somatic comorbidity, e.g. renal, hepatic, cardiac, neurological disorders Long-term use > 1 year Concurrent use with other CNS-active medicines (ATC groups N06A (antidepressants), N05A (antipsychotics), N05B (anxiolytics), or N05C (hypnotics))

Pharmacovigilance plan

The Marketing Authorisation Applicant has standard practices for routine pharmacovigilance activities involving spontaneous post-marketing adverse event reports, serious adverse events from clinical studies, pregnancy exposures, lactation exposures, overdoses and medication errors. Routine pharmacovigilance includes systems and processes to ensure that information about all suspected adverse reactions reported to the company is collected, the preparation of reports for regulatory authorities is made, and continuous monitoring of the safety profile of approved products is performed as described in *Pharmacovigilance System*.

All the safety concerns described in the safety specification will be adequately addressed by the standard pharmacovigilance activities as described above and the following additional pharmacovigilance activities:

- a. A non-interventional, multi-country, prospective cohort study (drug utilisation study) will provide data related to the patterns of use and of the frequency of selected adverse events in the overall treated population and in sub-populations in routine clinical practice.
- b. The drug utilisation study described above will be complemented by a parallel study, which will investigate the pattern of use of nalmefene in Europe by means of retrospective databases analyses.
- c. An interventional, single-site, open-label, four-group, single-dose study investigating the pharmacokinetic properties of nalmefene in subjects with renal impairment (mild, moderate, or severe) and in healthy subjects (to determine the AUC_{0-inf} of nalmefene and the main metabolite nalmefene 3-O-glucuronide following a single oral dose of 18 mg nalmefene in subjects with mild, moderate, or severe renal impairment and compare to that in healthy subjects).

Evaluation of the need for a risk minimisation plan

All the safety concerns described in the safety specification will be adequately addressed by routine risk minimisation. There is currently no additional risk minimisation activities planned.

Risk minimisation plan

Routine risk minimisation plan is summarised in the table below.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risks		
Confusional state, hallucination and dissociation	<ul style="list-style-type: none"> •Routine Pharmacovigilance •Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276) 	<p>Routine risk minimisation includes:</p> <p>Precaution in section 4.4 of the SmPC: <i>Psychiatric effects were reported in clinical studies (see section 4.8). If patients develop psychiatric symptoms that are not associated with treatment initiation with Selincro, and/or that are not transient, the prescriber should consider alternative causes of the symptoms and assess the need for continuing treatment with Selincro. Selincro has not been investigated in patients with unstable psychiatric disease. Caution should be exercised if Selincro is prescribed to patients with current psychiatric comorbidity such as Major Depressive Disorder.</i></p>
Concurrent use with opioids	<ul style="list-style-type: none"> •Routine Pharmacovigilance •Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276) •Use of Nalmefene in Europe: Databases analyses Study no: Not yet available (Company reference: REG_00032312) 	<p>Routine risk minimisation includes:</p> <p>Appropriate information in SmPC, section 4.3: <i>Patients taking opioid analgesics</i> <i>Patients with current or recent opioid addiction</i> <i>Patients with acute symptoms of opioid withdrawal</i> <i>Patients for whom recent use of opioids is suspected.</i></p> <p>Warning in section 4.4 in the SmPC: <u><i>Opioid administration</i></u> <i>In an emergency when opioids must be administered to a patient taking Selincro, the amount of opioid required to obtain the desired effect may be greater than usual. The patient should be closely monitored for symptoms of respiratory depression as a result of the opioid administration and for other adverse reactions. If opioids are needed in an emergency, the dose must always be titrated individually. If unusually large doses are required, close observation is necessary.</i></p> <p><i>Selincro should be temporarily discontinued for 1 week prior to the anticipated use of opioids, for example, if opioid analgesics might be used during elective surgery. The prescriber should advise patients that it is important to inform their Health Care Professional of last Selincro intake if opioid</i></p>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		<p><i>use becomes necessary.</i></p> <p><i>Caution should be exercised when using medicinal products containing opioids (for example, cough medicines, opioid analgesics (see section 4.5)).</i></p> <p>Information in section 4.5 of the SmPC: <i>If Selincro is taken concomitantly with opioid agonists (for example, certain types of cough and cold preparations, certain antidiarrhoeal preparations, and opioid analgesics), the patient may not benefit from the opioid agonist.</i></p>
Important Potential Risks		
Off-label use	<ul style="list-style-type: none"> •Routine Pharmacovigilance •Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276) •Use of Nalmefene in Europe: Databases analyses Study no: Not yet available (Company reference: REG_00032312) 	Routine risk minimisation is planned and considered adequate.
Important Missing Information		
Pregnant and lactating women	<ul style="list-style-type: none"> •Routine Pharmacovigilance •Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276) •Use of Nalmefene in Europe: Databases analyses Study no: Not yet 	<p>Routine risk minimisation activities include: Appropriate information in SmPC:</p> <p><i>Pregnancy</i> <i>There are no or limited data (fewer than 300 pregnancy outcomes) from the use of nalmefene in pregnant women.</i> <i>Animal studies have shown reproductive toxicity (see section 5.3).</i> <i>Selincro is not recommended during pregnancy</i></p> <p><i>Breast-feeding</i> <i>Available pharmacodynamic/toxicological data in animals have shown excretion of nalmefene or its metabolites in milk (see section 5.3). It is unknown whether nalmefene is excreted in human milk.</i></p>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
	<p>available (Company reference: REG_00032312)</p>	<p><i>A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Selincro therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.</i></p> <p><i>Fertility</i> <i>In fertility studies in rats, no effects were observed for nalmefene on fertility, mating, pregnancy, or sperm parameters.</i></p> <p>Section 5.3: <i>Studies in animals do not indicate direct harmful effects with respect to fertility, pregnancy, embryonic/foetal development, parturition, or postnatal development.</i> <i>In a rabbit embryo-foetal developmental toxicity study, effects on foetuses in terms of reduced foetal weight and delayed ossification, but no major abnormalities were seen. The AUC at the NOAEL for these effects was below the human exposure at the recommended clinical dose.</i> <i>An increase in still-born pups and decrease in post-natal viability of pups was observed in pre-postnatal toxicity studies in rats. This effect was considered to be an indirect effect related to toxicity to the dams.</i> <i>Studies in rats have shown excretion of nalmefene or its metabolites in milk.</i></p>
Children	<p>•Routine Pharmacovigilance</p> <p>•Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276)</p> <p>•Use of Nalmefene in Europe: Databases analyses Study no: Not yet available (Company reference: REG_00032312)</p>	<p>Routine risk minimisation activities include: Appropriate information in SmPC, stating that efficacy and safety have not been established for children and the use of Selincro is not recommended for this age group. A waiver for clinical data on the use of Selincro in children below age of 18 has been granted by the PDCO</p>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Genetic polymorphism	Routine Pharmacovigilance	Routine risk minimisation is planned and considered adequate. No studies are currently planned.
Other ethnic groups than Caucasian	<p>•Routine Pharmacovigilance</p> <p>•Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276)</p>	Routine risk minimisation is planned and considered adequate.
Overdose	<p>•Routine Pharmacovigilance</p> <p>•Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276)</p> <p>•Use of Nalmefene in Europe: Databases analyses Study no: Not yet available (Company reference: REG_00032312)</p>	<p>Routine risk minimisation activities include: Appropriate information in SmPC, stating: <i>In a study in patients diagnosed with pathological gambling, doses of nalmefene up to 90 mg/day for 16 weeks were investigated. In a study in patients with interstitial cystitis, 20 patients received 108 mg/day of nalmefene for more than 2 years. Intake of a single dose of 450 mg nalmefene has been reported without changes in blood pressure, heart rate, respiration rate, or body temperature. No unusual pattern of adverse events was observed in these settings, but experience is limited. Management of an overdose should be observational and symptomatic.</i></p>
Use in patients with increased (> 3x ULN) ALAT or ASAT	<p>•Routine Pharmacovigilance</p> <p>•Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276)</p>	<p>Routine risk minimisation activities include: Appropriate information in SmPC, section 4.4: <i>Caution should be exercised when prescribing Selincro to patients with elevated ALAT or ASAT (> 3 times ULN) as these patients were excluded from the clinical development programme.</i></p>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Use in patients with history of seizure disorder, including alcohol withdrawal seizures	<p>•Routine Pharmacovigilance</p> <p>•Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276)</p> <p>•Use of Nalmefene in Europe: Databases analyses Study no: Not yet available (Company reference: REG_00032312)</p>	<p>Routine risk minimisation activities include: Appropriate information in SmPC, section 4.3: <i>Patients with a recent history of acute alcohol withdrawal syndrome (including hallucinations, seizures, and delirium tremens).</i> Appropriate information in SmPC, section 4.4: <i>There is limited experience in patients with a history of seizure disorders, including alcohol withdrawal seizures.</i> <i>Caution is advised if treatment aimed at reduction of alcohol consumption is started in such patients.</i></p>
Use in elderly	<p>•Routine Pharmacovigilance</p> <p>•Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276)</p> <p>•Use of Nalmefene in Europe: Databases analyses Study no: Not yet available (Company reference: REG_00032312)</p>	<p>Routine risk minimisation activities include: Appropriate information in SmPC, section 4.2: <i>No dose adjustment is recommended for this patient population.</i> Precaution in section 4.4: <i>Limited clinical data are available on the use of Selincro in patients ≥ 65 years of age with alcohol dependence. Caution should be exercised when prescribing Selincro to patients ≥ 65 years of age.</i> Information in section 5.2: <i>No specific study with oral dosing has been conducted in patients ≥ 65 years of age. A study with intravenous administration suggested that there were no relevant changes in the pharmacokinetics in the elderly as compared to non-elderly adults. (see sections 4.2 and 5.2).</i></p>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Use in patients with significant psychiatric comorbidity	<p>•Routine Pharmacovigilance</p> <p>•Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276)</p> <p>•Use of Nalmefene in Europe: Databases analyses Study no: Not yet available (Company reference: REG_00032312)</p>	<p>Routine risk minimisation activities include: Appropriate information in SmPC, section 4.4: <i>Psychiatric effects were reported in clinical studies (see section 4.8). If patients develop psychiatric symptoms that are not associated with treatment initiation with Selincro, and/or that are not transient, the prescriber should consider alternative causes of the symptoms and assess the need for continuing treatment with Selincro. Selincro has not been investigated in patients with unstable psychiatric disease. Caution should be exercised if Selincro is prescribed to patients with current psychiatric comorbidity such as Major Depressive Disorder.</i></p>
	<p>•Routine Pharmacovigilance</p> <p>•Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276)</p> <p>•Use of Nalmefene in Europe: Databases analyses Study no: Not yet available (Company reference: REG_00032312)</p>	<p>Routine risk minimisation includes: Appropriate information in SmPC, section 4.3: <i>Patients with a recent history of acute alcohol withdrawal syndrome (including hallucinations, seizures, and delirium tremens).</i> Appropriate information in SmPC section 4.4: <i>There is limited experience in patients with a history of seizure disorders, including alcohol withdrawal seizures. Caution is advised if treatment aimed at reduction of alcohol consumption is started in such patients. Selincro is extensively metabolised by the liver and excreted predominantly in the urine. Therefore, caution should be exercised when prescribing Selincro to patients with mild or moderate hepatic or mild or moderate renal impairment, for example, by more frequent monitoring.</i></p>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Long-term use >1 year	<ul style="list-style-type: none"> •Routine Pharmacovigilance •Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276) •Use of Nalmefene in Europe: Databases analyses Study no: Not yet available (Company reference: REG_00032312) 	<p>Routine risk minimisation includes: Appropriate information in SmPC, section 4.2: <i>During pivotal trials the greatest improvement was observed within the first 4 weeks. The patient's response to treatment and the need for continued pharmacotherapy should be evaluated on a regular (for example, monthly) basis. The physician should continue to assess the patient's progress in reducing alcohol consumption, overall functioning, treatment adherence, and any potential side effects. Clinical data for the use of Selincro under randomised controlled conditions are available for a period of 6 to 12 months. Caution is advised if Selincro is prescribed for more than 1 year.</i></p> <p>Appropriate information in SmPC, section 4.4: <i>There is limited experience in long term treatment beyond 1 year in patients. Caution is advised if Selincro is prescribed for more than 1 year.</i></p>
Concurrent use of other CNS-active medicines	<ul style="list-style-type: none"> •Routine Pharmacovigilance •Non-interventional multi-country prospective cohort study to investigate the pattern of use of Selincro and frequency of selected adverse drug reactions in routine clinical practice Study no: 14910A (Company reference: REG_00030276) •Use of Nalmefene in Europe: Databases analyses Study no: Not yet available (Company reference: REG_00032312) 	<p>Routine risk minimisation includes: Appropriate information in SmPC, section 4.5 stating that no <i>in vivo</i> drug-drug interaction studies have been conducted and describing the potential kinetic interactions.</p>

The CHMP endorsed this risk management plan.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

Benefits

Beneficial effects

An overall reduction from baseline of drinking amounts was noted within the clinical trial setting. The baseline number of HDDs of 19.3 per month was reduced by about 11-12 days in the NMF group in the overall population. Equally, Total alcohol consumption (87.7 g/d at baseline) was reduced by about 50g.

The results for the secondary responder analysis are concordant with the results for the co-primary reduction of HDD and TAC. Following the MMRM approach, odds ratios for showing 30%, 50% or 70% reduction in TAC after 24 weeks of treatment were significantly favourable to NMF as compared to placebo in the pooled FAS. 86.1% of subjects receiving NMF reduced alcohol consumption by 30% (70.9% of subjects achieved 50% reduction, 46.8% reduced drinking by 70%). However, placebo response was high and consistent.

In the subgroup of patients with a *high* or *very high* DRL at baseline and randomisation (50% of the total population) the treatment effect in terms of HDD/TAC reduction and associated responder analyses was more pronounced (HDDs [MMRM, Diff (95%CI; p)], study 12014A: -3.7 (-5.9,-1.5; <0.001), study 12023A: -2.7 (-5.0,-0.3; 0.025) (TAC [MMRM, Diff (95%CI; p] study 12014A: -18.3 (-26.9, -9.7; <0.001), study 12023A: -10.3 (-20.2, -0.5; 0.040).

Uncertainty in the knowledge about the beneficial effects

In the total population, the difference in treatment effect between nalmefene and placebo (equivalent to BRENDA only) was small, not consistently statistically significant across co-primary endpoints, and of questionable clinical relevance (HDDs [MMRM, Diff (95%CI; p)], study 12014A: -2.3 (-3.8,-0.9; 0.002), study 12023A: -1.7 (-3.1,-0.4; 0.012) (TAC [MMRM, Diff (95%CI; p], study 12014A: -11.0 (-16.8, -5.1; <0.01), study 12023A: -4.9 (-10.6, 0.7; 0.088).

The positive tendency and the order of magnitude of parameters showing persistence of the treatment effect over 13 months (reduction of drinking days despite IMP intake, increase of study adherence, reduction of days with no IMP Intake and drinking, and increasing portion of abstinent days with no IMP intake) was similar in patients receiving placebo. The favourable development (both for placebo and NMF) may be explained by the increasing accumulation of study completers (mostly responders) in the course of the 13 months.

The proportion of patients who withdrew was high in the Alcohol Dependence Pool (33.9% in the placebo group and 42.9% in the nalmefene group). Withdrawal of consent was the primary reason for withdrawal for 13.3% of the patients in the placebo group and for 15.7% of the patients in the nalmefene group and was the most common primary reason in both treatment groups.

For 3.8% of the patients in the placebo group and 10.5% of the patients in the nalmefene group, the primary reason for withdrawal was adverse events.

The high withdrawal rate renders imputation of missing data an important issue when determining statistical significance of primary efficacy endpoints. This was tried to resolve by sensitivity analyses applying various imputation methods (MMRM, PMI, LOCF, BOCF etc). Whereas most sensitivity

analyses confirmed the primary analysis, a treatment effect of verum vs. placebo was absent in the BOCF analysis.

Risks

Unfavourable effects

The incidence of TEAEs was high after nalmefene administration (74.7%). Additionally, study discontinuation due to intolerable AEs was high (10.5%), and may still be underestimated, since for a number of patients discontinuing for consent withdrawal the occurrence of AEs may well play a contributory role. TEAEs mainly occurred early at treatment initiation. In the further course of treatment tolerability improves. Mostly, TEAEs were rather unspecific like nausea or dizziness. Many patients reported sleep-related events (either at day- or night-time). However, apart from actual substance-related effects on sleep, the reduction of alcohol amounts is also thought to interfere with sleep as a sign of mild withdrawal at treatment initiation.

Nalmefene did not appear to additionally compromise hepatic function on top of alcohol-related liver enzyme increases.

Occurrence of TEAEs was mostly related to the intake of nalmefene itself, rather than the combination of nalmefene with alcohol. However, nalmefene may also deter patients from drinking by causing unspecific symptoms like nausea, dizziness etc. before alcohol is actually taken.

Overall, there were no serious adverse events causing major safety concern.

Uncertainty in the knowledge about the unfavourable effects

The influence of hepatic and renal impairment on the pharmacokinetics of nalmefene after oral administration of 18 mg doses was not fully elucidated. Data on the use of nalmefene in patients with severe hepatic impairment are missing. Selincro is contraindicated in patients with severe renal or severe hepatic impairment.

Based on the available data, differentiated dose recommendations or warning notes for various degrees of renal or hepatic impairment could not be formulated. This is reflected in Sections 4.2 of the SmPC. Section 4.4 of the SmPC states that caution should be exercised when prescribing Selincro to patients with mild or moderate hepatic or mild or moderate renal impairment, for example, by more frequent monitoring.

A study investigating the pharmacokinetic properties of nalmefene in subjects with renal impairment (mild, moderate, or severe) and in healthy subjects will be carried out as part of the pharmacovigilance activities.

Selincro has not been investigated in patients with unstable psychiatric disease. The SmPC recommends caution if Selincro is prescribed to patients with current psychiatric comorbidity such as major depressive disorder.

Benefit-risk balance

Interpretation of efficacy results observed for the Full Analysis Set was complicated by the fact that a considerable number of subjects almost entirely finished drinking during the 1-2 week time period

between screening and randomisation. In these pre-random-reducers there was virtually no space for further improvement either by BRENDA interventions or IMP intake.

A *post-hoc* analysis identified the population in which the efficacy of nalmefene was demonstrated: those patients with *high* or *very high* drinking risk level (DRL) at baseline and maintained this risk level at randomisation. To reflect this, the indications specify that Selincro should be initiated only in patients who continue to have a high DRL two weeks after initial assessment.

In this subgroup, identified as most likely to benefit, the net treatment effect over placebo in terms of Heavy Drinking Day (HDD) reduction was more pronounced.

Overall, there were no serious adverse events causing major safety concern.

Discussion on the benefit-risk balance

The overall B/R of nalmefene 18 mg tablets (Selincro) is positive, given the demonstrated clinical benefit in the defined subgroup of target population and taking into account that particular safety concerns were not raised over the 1-year treatment period.

The CHMP recommended the following wording for SmPC section 4.1 as the one that would most accurately reflect the pivotal trial data and specify the target population and prescribing conditions most appropriate for nalmefene treatment:

Selincro is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (see section 5.1), without physical withdrawal symptoms and who do not require immediate detoxification.

Selincro should only be prescribed in conjunction with continuous psychosocial support focussed on treatment adherence and reducing alcohol consumption.

Selincro should be initiated only in patients who continue to have a high drinking risk level two weeks after initial assessment.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Selincro in the treatment of *the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (see section 5.1), without physical withdrawal symptoms and who do not require immediate detoxification* is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that nalmefene is qualified as a new active substance.

Nalmefene hydrochloride dihydrate is structurally related to Naltrexone hydrochloride which has been already authorized in the EU. Naltrexone (base) but not the approved Naltrexone hydrochloride is used as a precursor during the synthesis of Nalmefene hydrochloride dihydrate. Naltrexone (base) is transformed into Nalmefene (base) by a formal substitution of a carbonyl group's oxygen ($R_1R_2C=O$) with a methylene functionality ($R_1R_2C=CH_2$) which leads to a substantial change in molecular structure and to a significant modification of chemical as well as physico-chemical properties. As a consequence of these attributes different pharmacokinetic, pharmacodynamic and toxicological properties have to be expected. Therefore, Nalmefene hydrochloride dihydrate can not be considered as a derivative of an authorized substance.

APPENDIX
DIVERGENT POSITION

Divergent position

In the two pivotal studies supporting the indication the treatment effect is modest. The difference in treatment effect between nalmefene and placebo (equivalent to BRENDA only) is not consistently statistically significant across co-primary endpoints, and of questionable clinical relevance in the total population.

In this pivotal studies 12014A and 12023A, 18%, and 33%, of the patients, respectively, considerably reduced their alcohol consumption in the period between screening and randomisation. Therefore, the patients who maintained a high or very high DRL at randomisation were defined post-hoc as the target population.

In the post-hoc subgroup of patients with a high or very high DRL at baseline and randomisation (50% of the total population)' the treatment effect in terms of HDD/TAC reduction and associated responder analyses was slightly higher but still modest.

Due to the high number of withdrawals a number of sensitivity analyses were conducted. The reduction in alcohol consumption in terms of reduction in HDDs and TAC was inconsistent across the various sensitivity analyses. The Biostatistics Working Party concluded that multiple imputation (MI) analysis is the most relevant analysis to answer this question but the robustness of treatment effect is not supported by this sensitivity analysis.

There was an inconsistent response across both studies in terms of the clinically relevant improvements in liver biomarkers and health-related quality-of-life scale scores.

There is no direct evidence of harm reduction. The applicant provided modelling of epidemiological data. However, during CHMP discussions the assumptions upon which these studies and modellings were based were not unanimously supported.

The treatment effect observed in the pivotal studies translates into approximately 2 fewer HDDs per month and 1-2 drinks fewer per day for patients treated with nalmefene compared to those who received placebo (MMRM analysis). The majority of participants continued to have significant levels of HDDs and daily levels of consumption of alcohol. The clinical significance of this modest reduction in alcohol consumption has not been demonstrated in these studies.

London, 13 December 2012

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