Nalmefene for reducing alcohol consumption in people with alcohol dependence: A Single Technology Appraisal

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Matt Stevenson and Andrew Rawdin critiqued the mathematical model provided and the cost-effectiveness analyses submitted by the manufacturer. Abdullah Pandor critiqued the clinical effectiveness data reported by the manufacturer. John Stevens critiqued the statistical analyses undertaken by the manufacturer. Ruth Wong undertook the literature searches run by the ERG. Marsha Morgan, Peter Rice, and Jez Thompson provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final document.

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Abbreviations

AD	Alcohol Dependence
AUDIT	Alcohol Use Disorders Identification Test
CI	Confidence Interval
DRL	Drinking Risk Level
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
EMA	European Medicines Agency
ERG	Evidence Review Group
GP	General Practitioner
HRQoL	Health-Related Quality Of Life
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention To Treat
LY	Life Years
MS	Manufacturer's Submission
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NMF	Nalmefene
PASS	Post-Authorisation Safety Study
PI	Psychosocial Intervention
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
QALY	Quality Adjusted Life Years
RCTs	Randomised Controlled Trials
RR	Relative Risk
SADQ	Severity of Alcohol Dependence Questionnaire
STA	Single Technology Appraisal
WHO	World Health Organisation
WTP	Willingness To Pay

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The population considered within the manufacturer's submission (MS), as defined in the scope, is 'Adults with mild alcohol dependence (as defined in NICE Clinical Guideline 115 [CG115]) who have a high drinking risk level (≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification and continue to have a high drinking risk level 2 weeks after initial assessment.'

The final scope stated that the intervention (nalmefene) and one of the two comparators (naltrexone) be used in conjunction with psychosocial intervention (PI) as defined in NICE CG115, with such PI being the remaining comparator. The main analysis within the MS is an analysis of the cost-effectiveness of the addition of nalmefene to a PI of lower intensity than recommended in NICE CG115; this has been termed Comparison 1 by the Evidence Review Group (ERG). The manufacturer attempts to address the lack of comparison with PI as recommended in NICE CG115 via a threshold analysis which estimates the reduction in the benefit associated with nalmefene necessary to reach cost per quality adjusted life years (QALY) of £20,000 and £30,000. This has been termed Comparison 2 by the ERG. The manufacturer did not comment on the likely cost-effectiveness of delayed initiation of nalmefene for those who did not respond to PI as recommended in NICE CG115 compared with immediate initiation of nalmefene for all patients. Delayed use of nalmefene would be aligned with the recommendation for pharmacotherapy in NICE CG115, although this guideline was written before the licensing of nalmefene. This has been termed Comparison 3 by the ERG. In addition the manufacturer did not comment on the likely cost-effectiveness of nalmefene use (delayed or immediate) with the use of off-label naltrexone, following informed consent being obtained, as recommended in NICE CG115. This has been termed Comparison 4 by the ERG.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The MS included a systematic review of the clinical effectiveness literature. The main supporting evidence was derived from three manufacturer-sponsored, multi-country, multi-centre, randomised, double-blind, parallel-group, placebo-controlled European phase III clinical trials that compared the use of nalmefene with placebo. In all three studies, patients in the treatment and placebo groups received motivational and adherence-enhancing PI sessions (termed BRENDA), which were provided by trained personnel such as investigators, nurses and psychologists. The ESENSE1 (n=604) and ESENSE2 (n=718) trials were 24 weeks studies whereas the SENSE (n=675) trial was a 52 week study.

The manufacturer's primary post-hoc subgroup meta-analysis (a conventional pairwise comparison) of those with a high or very high drinking risk level at baseline and randomisation (i.e. the licensed

population group judged to benefit the most from nalmefene treatment) showed [redacted]

In the licensed population in the ESENSE1, ESENSE2 and SENSE trials higher rates of patient withdrawal were observed in the pooled nalmefene plus PI group (224/475 [47.2%]) compared with the placebo plus PI group (133/ 369 [36.0%]). The main reasons for study discontinuation were withdrawal of consent and adverse events. Treatment emergent adverse events leading to withdrawal occurred in [redacted] patients in the pooled nalmefene plus PI group compared with [redacted] patients in the pooled placebo plus PI group.

In the pooled subgroup of people with at least a high drinking risk level at screening and randomisation (licensed population), the incidence of treatment emergent adverse events was more frequent in the nalmefene plus PI group (368/475 [77.5%]) than in the placebo plus PI (246/369 [66.7%]). The most common treatment-related adverse events in the nalmefene plus PI group were nausea (24.2% versus 6.5%), dizziness (21.9% versus 6.0%), insomnia (14.5% versus 4.3%) and headache (12.6% versus 9.5%) compared with placebo plus PI, respectively. The onset of the most frequent adverse events in the nalmefene plus PI group occurred within a day of the first dose for nausea, dizziness, fatigue, and somnolence and within approximately 1 week for insomnia, headache, and vomiting. The duration was typically a few days (the median duration was ≤ 8 days for all the frequent adverse events in the nalmefene group). In the total population in the ESENSE1, ESENSE2 and SENSE trials, the incidence of treatment emergent adverse events was similar to that observed for the licensed population (855/1144 [74.7%] versus 500/797 [62.7%], respectively). The incidence of serious adverse events (no definition was provided in the MS) in the pooled subgroup of people with at least a high drinking risk level at screening and randomisation (licensed population) was higher in the nalmefene plus PI group (26/475 [5.5%]) compared with the placebo plus PI (13/369 [3.5%]) group. Similar results were observed for the total population (57/1144 [5.0%] versus 35/797 [4.4%], respectively).

In the absence of any direct head-to-head randomised controlled trials (RCTs) comparing nalmefene plus PI with naltrexone plus PI, the manufacturer determined whether a network meta-analysis could be conducted to investigate the effect of naltrexone plus PI with nalmefene plus PI for the reduction of

alcohol consumption in actively drinking adults with mild alcohol dependence. The manufacturer's systematic review identified three RCTs; however, all identified studies had limitations in the reporting of data (not reporting values for total alcohol consumption, not reporting drinking levels at baselines, lack of reported data for the drinking outcomes and not reporting the evaluable number of patients) thus making them ineligible for inclusion in a network meta-analysis.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review process followed by the manufacturer was comprehensive. Despite minor limitations in the manufacturer's search strategy, the ERG is confident that all relevant studies of the intervention (nalmefene plus PI) and comparator (naltrexone plus PI) were included in the MS (including details of ongoing studies). The specified inclusion and exclusion criteria are (mostly) appropriate and generally reflect the information given in the decision problem. However, studies that included alcohol dependent people with co-morbid disorders (e.g. schizophrenia or bipolar disorder) or a co-addiction (e.g. cocaine co-dependency or pathologic gambling) were excluded. Although no reason or rationale for exclusion was provided by the manufacturer, the ERG noted that many alcohol-dependent patients have diagnosed medical conditions and/or psychiatric co-morbidities. The validity assessment tool used to appraise the included studies was based on the quality assessment criteria for RCTs and was considered appropriate by the ERG.

Although the efficacy and safety of nalmefene plus PI was positively demonstrated (compared with placebo plus PI) in the included studies, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Due to the post-hoc subgroup analyses and high dropout rates in the three nalmefene studies inference of treatment effects (including magnitude) may be confounded. In the systematic review of the relevant comparators (i.e. naltrexone), all three included studies had limitations in reporting of outcome data thus making them ineligible for inclusion in a network meta-analysis. However, the manufacturer made no attempt to contact authors of the included naltrexone studies for potential unpublished data.

The key uncertainties in the clinical evidence relate to different types or frequencies of PI, duration of treatment and generalisability to the UK population.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer submitted a cohort Markov model with a time horizon of 5 years populated with data pooled from the ESENSE1, ESENSE2 and SENSE trials. Treatment with nalmefene plus PI or with PI alone was assumed to be for a period of 12 months. In the base case those patients drinking at a high- or very high- risk level after 12 months would be offered medically assisted withdrawal and subsequent treatment with naltrexone or acamprosate, although this option could be removed within the model.

For Comparison 1 the manufacturer estimated that nalmefene and PI dominated PI, that is nalmefene and PI was cheaper and more effective than PI alone; the conclusion that nalmefene plus PI was more cost-effective than PI alone was robust in all sensitivity analyses undertaken. For Comparison 2, the manufacturer estimated that the benefit of adding nalmefene to low-intensity PI would need to be reduced by 70% to obtain a cost per QALY of £20,000 and by 77% to obtain a cost per QALY of £30,000. No comments on the cost-effectiveness of nalmefene in addition to PI in Comparisons 3 or 4 were provided by the manufacturer.

Superseded – see Erratum

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considered the model submitted by the manufacturer to be generally well-constructed with the majority of assumptions being unfavourable, rather than favourable, to nalmefene, although half-cycle correction was not undertaken. In the model it was assumed that all patients who failed to respond to nalmefene and PI would need medically assisted withdrawal from alcohol which the clinical advisors to the ERG considered unlikely and hence inappropriate. There was no allowance within the model for these individuals to receive additional specialist input and hence it is unclear how the incorporation of such specialist input at an earlier time would impact on the cost-effectiveness of nalmefene. The costs of serious and temporary events included in the model do not appear to be those in the cited source although this potential error was unfavourable to nalmefene. The largest limitation was that no formal comparison of nalmefene plus PI compared with PI alone, where PI was that recommended by NICE CG115.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The manufacturer undertook a comprehensive systematic review (no major limitations were noted) of nalmefene for the reduction of alcohol consumption in people with alcohol dependence. The ESENSE1, ESENSE2 and SENSE trials were of reasonable methodological quality (with some limitations) and measured a range of clinically relevant outcomes.

The mathematical model submitted by the manufacturer had few errors and appeared well-constructed. The manufacturer acknowledged that the PI undertaken in the RCTs did not meet the requirements recommended in NICE CG115 and undertook a threshold analysis to assess the level of reduction in the efficacy benefit required to produce cost per QALY values of £20,000 and £30,000.

1.6.2 Weaknesses and areas of uncertainty

The pivotal RCTs of nalmefene in addition to PI compared with PI alone use PI in the form of BRENDA which is less intensive than PI recommended in NICE CG115. The small number of UK patients in these studies means that the generalisability to England and Wales is unclear. There are no head-to-head RCTs comparing nalmefene plus PI with naltrexone plus PI.

The model did not incorporate a half cycle correction. The manufacturer assumed that patients would remain on their initial treatment for a period of 12 months without increasing the intensity of PI where necessary. Large areas of uncertainties are that there are few robust data to inform Comparisons 2, Comparison 3 and Comparison 4: all of which the ERG believes to be highly relevant.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made a small number of changes to the manufacturer's base case scenarios although this did not affect the conclusions. In Comparison 1, nalmefene in addition to low-intensity PI was estimated to dominate low-intensity PI. In Comparison 2, the threshold values estimated by the ERG were lower than that estimated by the manufacturer, at 63% to result in a cost per QALY of £20,000 and 72% to result in a cost per QALY of £30,000. For Comparison 3, the ERG ventured that delayed nalmefene is probably a more cost-effective approach than immediate nalmefene for all patients. The rationale for this statement was that with low-intensity PI data from the pivotal trials indicate that approximately 20% of patients had low-risk drinking levels or were abstinent at month 3, a value that would be expected to be higher if the PI used were that recommended in NICE CG115. However, the ERG acknowledges that ideal data for this comparison do not exist. For Comparison 4, there are no data regarding the relative effectiveness of either nalmefene or naltrexone with which to provide an informed estimate of the incremental cost per QALY gained.

2 BACKGROUND

This report provides a review of the evidence submitted by Lundbeck Limited in support of oral nalmefene (in conjunction with continuous psychosocial support/ intervention [PI]) for the reduction of alcohol consumption in people with mild alcohol dependence who do not require medically assisted withdrawal from alcohol. It considers both the original submission received on the 4th March 2014 and a subsequent response to clarification questions supplied by Lundbeck Limited on the 7th April 2014.

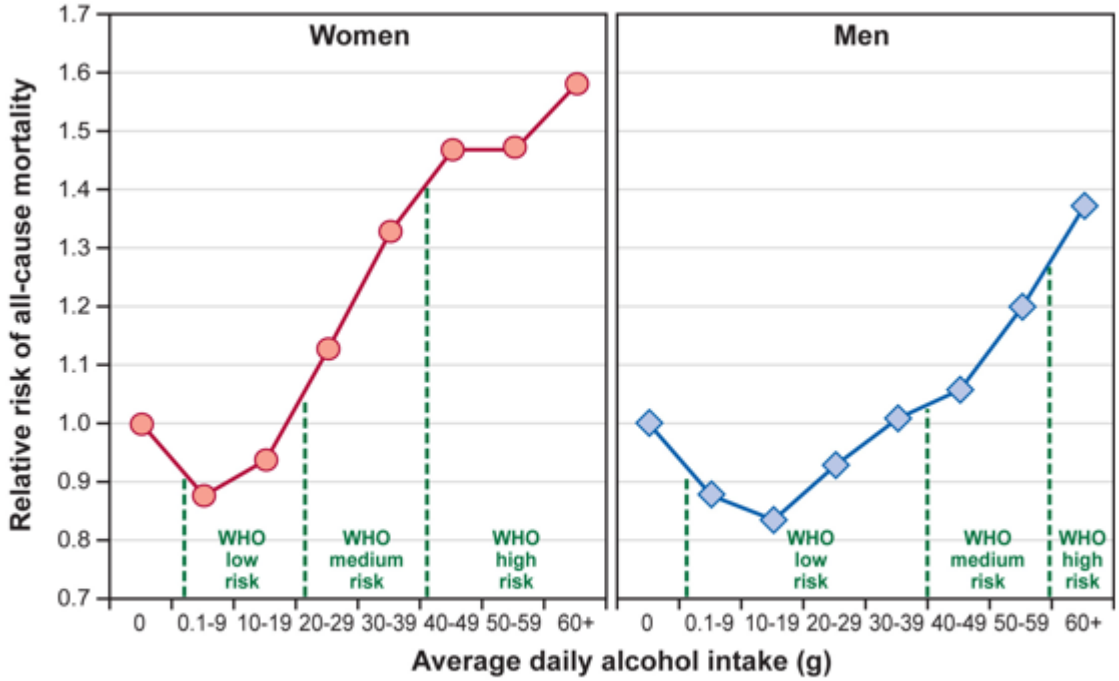
2.1 Critique of manufacturer's description of the underlying health problem

The manufacturer provided a good description of the underlying health problem, which is summarised in this section. Alcohol dependence is a central nervous system disorder and is associated with characteristic structural and functional changes in the brain of alcohol-dependent patients that over time leads to compulsive drinking.[1] Estimates of the overall prevalence of alcohol dependence in England vary from approximately 4% to 6%.[2-4] resulting in an estimated 1.6 million people who are alcohol dependent in England and approximately 140,000 in Wales.[5]

Alcohol dependence has a high probability of a chronic and progressive course and places a large burden on individual health and society, which rises with increasing alcohol consumption.[6] In 2004, alcohol dependence accounted for more than 70% of the overall alcohol-attributable net mortality before the age of 65 years in the European Union.[7] As shown in Figure 1, a reproduction of Figure A2 from the manufacturer's submission (MS), the relative risk for all-cause mortality is highest among patients with the highest average daily intake of alcohol. The manufacturer has cited the values as being adapted from English *et al*.[8]

The categories in Figure 1 relate to those defined by the World Health Organisation (WHO). These are shown in Table 1 together with the average alcohol intake per day associated with each category.

Figure 1: Relative risk for all-cause mortality by average daily intake of alcohol



WHO = World Health Organization.

Table 1: Categories of drinking risk levels and daily alcohol consumption in each category[a]

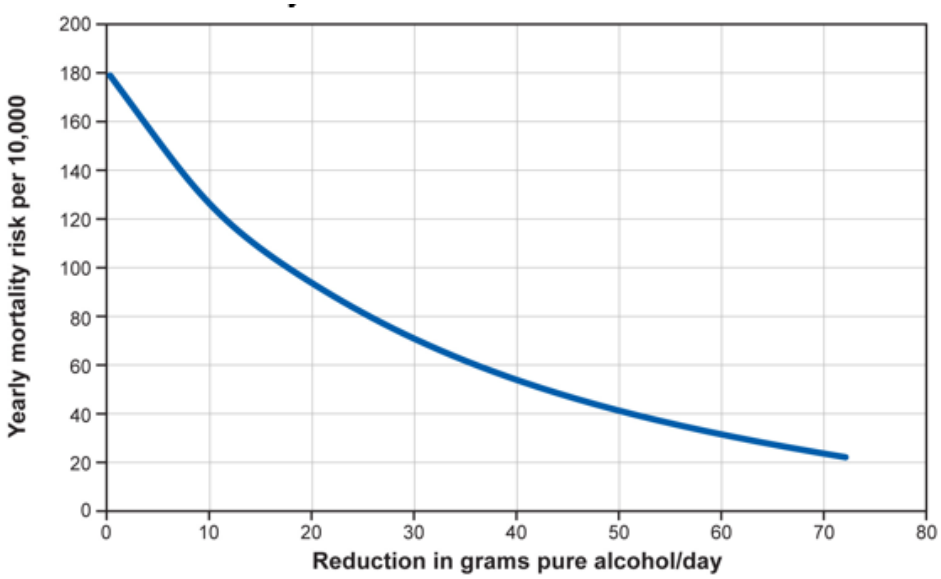
Drinking Risk Level	Females	Males
Very High Risk	>61g	> 101 g
High Risk	41 to 60g	61 to 100g
Medium Risk	21 to 40g	41 to 60g
Low Risk	1 to 20g	1 to 40g
Abstinent	<1g	<1g

[a] One UK unit equals 8g of pure alcohol

Reduction of drinking, especially of heavy drinking, is associated with a reduction in alcohol-attributable mortality, with the reduction being highest for the heaviest drinking category.[9] Figure 2 reproduces Figure A3 from the MS, which is sourced from Rehm and Roerecke,[9] and provides an indication of the mortality benefits associated with a reduction in alcohol consumption in heavy drinkers. A further estimate of the impact of morbidity and mortality due to alcohol dependence was

provided in Rehm *et al.*[7] which reported 563 disability-adjusted life-years and 23 years of life lost per 100,000 people.

Figure 2: Relationship between alcohol consumption reduction in heavy drinkers and mortality risk



Source: Rehm and Roerecke, 2013.

In addition to the impact on mortality, alcohol dependence is also associated with many serious social issues, including family problems, parenting problems, and lost productivity in the workplace.[7]

2.2 Critique of manufacturer's overview of current service provision

The manufacturer, in general, provided a reasonable overview of current service provision although the clinical advisors to the Evidence Review Group (ERG) believed that the level of expertise required by the clinician and the relative intensity of PI stated by the manufacturer did not represent best practice and were not aligned with the guideline issued by NICE in 2011 on the management of alcohol dependence and harmful alcohol use (NICE CG115).[3]

The manufacturer states that of the people who are alcohol dependent only approximately 6% per year receive treatment.[4,10] Reasons for this include the often long period between developing alcohol dependence and seeking help and the limited availability of specialist alcohol treatment services in some parts of England.[3] The mainstay of treatment for people with mild alcohol dependence are PI techniques which have been shown to be effective in both reducing alcohol consumption and maintaining abstinence.[3] NICE CG115 recommends cognitive behavioural therapies, social network and environment based therapies and, where appropriate, behavioural couples therapy, in patients with

mild dependence. However, the manufacturer states (p108 and 109 of the MS) that in response to a survey that brief interventions are the mainstay of treatment for alcohol dependence in primary and specialist care in England The respondents were said to be more than 20 primary care practices and specialist alcohol centres/addiction clinics from across England; no response rate was provided. The ERG comments that even were brief interventions representative of current practice the final scope issued by NICE was explicit that PI was that as defined in NICE CG115.

The current NICE guideline (CG115) recommends a treatment goal of either abstinence or reduction of alcohol consumption, depending on the severity of alcohol dependence.[3] However, NICE CG115 also makes a number of statements that the clinical advisors to the ERG believed were not sufficiently stressed within the MS. These include:

1) All interventions for people who misuse alcohol should be delivered by appropriately trained and competent staff (Section 6.24.1.4 of NICE CG115).
2) PI, including behavioural therapies, cognitive behavioural therapy and behavioural couples therapies would consist typically of weekly sessions of 1 hour's duration over a 12-week period and be delivered typically by a clinical psychologist (Sections 6.24.1.15 – 6.24.1.18 and Table 85 of NICE CG115). The evidence base for the delivery and timings of PI in NICE CG115 were based on the reviewed evidence and expert opinion of the guideline development group, and thus were considered to be reflective of what should be delivered in the UK NHS. With respect to the duration of treatment NICE CG115 states that 'The duration of treatment and number of sessions across the treatment trials included in the review was also considered. The duration of treatment for motivational techniques was 1 to 6 weeks, twelve step facilitation was 12 weeks, cognitive behavioural therapies was 2 weeks to 6 months (with most ending at 12 weeks), behavioural therapies was 6 to 12 weeks, social network and environment-based therapies ranged from 8 to 16 weeks, and couples therapies ranged from 4 to 12 weeks. Taking into consideration the intensity of the treatments in these trials, for those with a high-intensity intervention, the duration of treatment was on average 12 weeks. It was acknowledged by the clinical advisors to the ERG that some patients may require less PI input, whereas others may need more. The main constraints in provision at this level would be access and finance. These treatments are relevant for this decision as the population considered in NICE CG115 were harmful drinkers who might be mildly dependent who were treatment seeking. BRENDA, by contrast is not a stand-alone treatment, but is designed to be used in conjunction with medication for the treatment of addiction, and once mastered can be administered in as little as 15 minutes.[11] As noted in the MS (p108) BRENDA most closely resembles a planned brief intervention or motivational intervention. NICE CG115 states (p30) that 'Screening and brief intervention delivered by a non-specialist practitioner is a cost-effective approach for hazardous and harmful drinkers (NICE, 2010a[12]). However, for people

who are alcohol dependent, brief interventions are less effective and referral to a specialist service is likely to be necessary (Moyer *et al*., 2002[13]). It is important, therefore, that health and social care professionals are able to identify and appropriately refer harmful drinkers who do not respond to brief interventions, and those who are alcohol dependent, to appropriate specialist services.'

3) That currently pharmacological intervention would be considered for use in patients with mild alcohol dependence only in those who had not responded to PI or those who have specifically requested a pharmacological intervention (Section 7.16.5 of NICE CG115). The ERG acknowledges that NICE CG115 was written before nalmefene was licensed, but notes that it is a plausible strategy that nalmefene, in those who have not requested a pharmacological intervention, be reserved for those who have not adequately responded to PI. A clinical advisor to the ERG stated that a possible reason as to why PI is recommended first-line in CG115 is that the techniques recommended can change a person's approach to their addiction problem and hence their behaviour. PI can teach coping skills which can be called on in the future to help maintain abstinence whereas pharmacological interventions do not change behaviour.

Superseded – see Erratum

The implications of these statements for this Single Technology Appraisal (STA) will be discussed later in the document at appropriate points.

For a patient whose condition worsens to such a level that detoxification is required NICE CG115 recommends that patients with moderate and severe alcohol dependence should have an immediate treatment goal of abstinence; these patients should undergo detoxification via a medically assisted alcohol withdrawal programme. After successful completion of the alcohol withdrawal programme, the physician may consider pharmacotherapy together with ongoing PI to assist in maintaining abstinence. In these cases the manufacturer assumed that treatment with naltrexone, acamprosate or disulfiram could be provided.

The diagram of current service provision as provided by the manufacturer (Figure A4, p45 of the MS) is replicated in Figure 3 and the manufacturer's proposed placement of nalmefene in the service pathway (Figure A5, p46 of the MS) is reproduced in Figure 4. It can be seen that the use of nalmefene is proposed only for those who are still drinking at high-risk levels two weeks following a brief intervention. The manufacturer only appraises two alternatives, namely nalmefene plus PI, and PI alone: there is no consideration of nalmefene being provided only to non-responders to PI, or

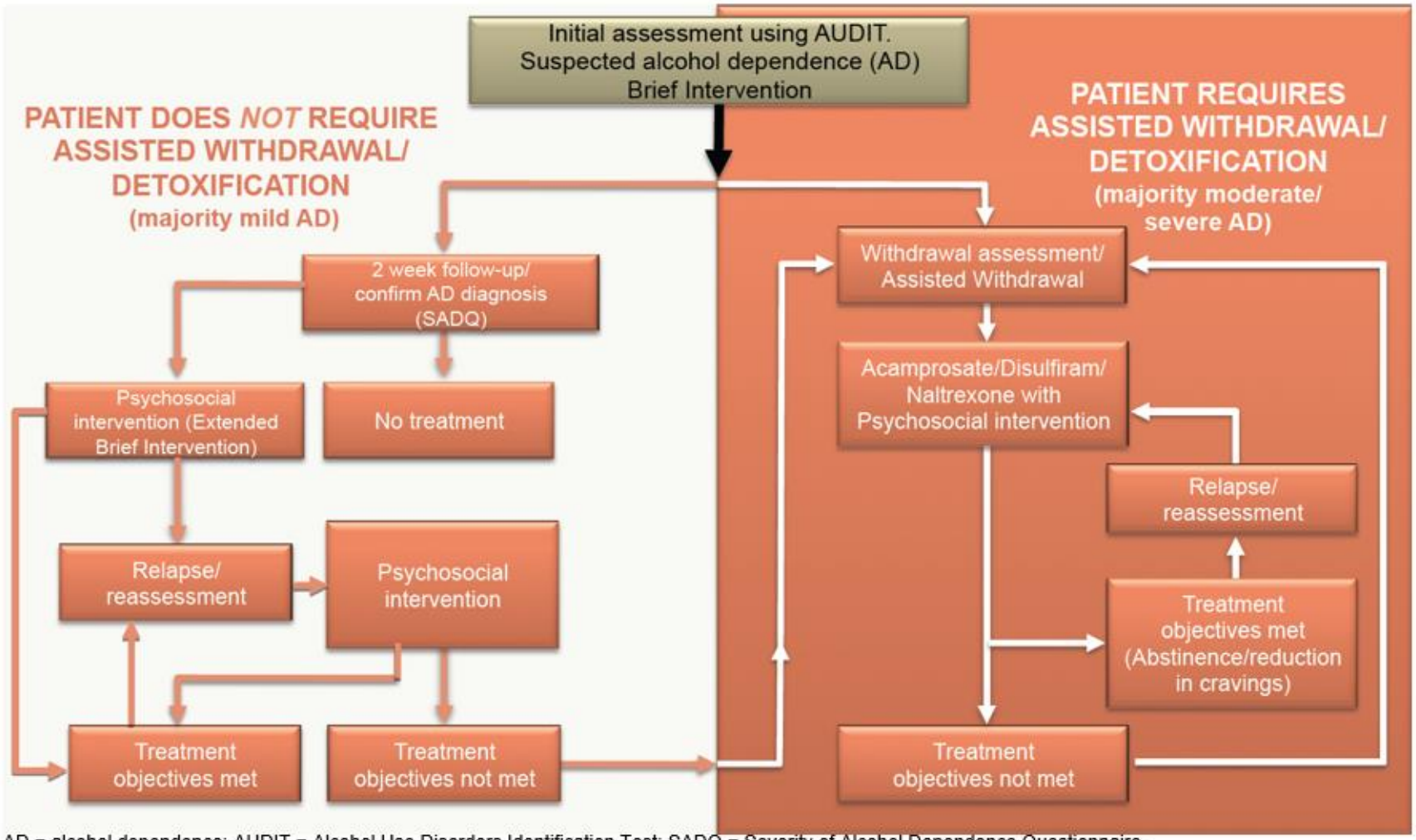
consideration of naltrexone being used prior to medically assisted withdrawal. One of the clinical advisors to the ERG commented that the 'treatment objectives not met box' would not necessarily lead to medically assisted withdrawal and that there should be a possibility of such patients being re-assessed with the Severity of Alcohol Dependence Questionnaire (SADQ) and if not in need of medically assisted withdrawal being treated with an alternative pharmacological agent or more intensive PI. This assumption is likely to be favourable to nalmefene as the costs associated with medically assisted withdrawal are not insignificant.

The ERG also notes that for those people without alcohol dependency in Figure 3, no treatment may be replaced with some form of PI, if patients were still drinking. However, this would not affect the decision problem considered here. The same statement is made regarding the low / medium drinking risk level in Figure 4.

Figure 3 is in essence an amalgamation of Figures 5 and 6 from NICE CG115; pages 146 and 150 of NICE CG115 respectively. Figure 5 of NICE CG115 segregates the further action required based on Alcohol Use Disorders Identification Test (AUDIT) score: <8 requiring no further action; 8-15 a brief intervention; 16-19 an extended brief intervention with referral to specialist assessment if there was no improvement; and 20 or greater where there is referral to specialist assessment to determine if immediate withdrawal is required. If the AUDIT score is less than 20 then PI alone is recommended, with a comprehensive assessment if co-morbid features are present. If the AUDIT score is 20 or greater, the patient should be assessed further, with Figure 6 of NICE CG115 categorising the outcome of the assessment in terms of dependence severity with the SADQ or number of units per typical drinking day. Patients with SADQ scores less than 15 have the same recommendations as those with an AUDIT score below 20, patients with SADQ scores of 15-30 without comorbid features are recommended to receive outpatient medically assisted withdrawal, whilst the remaining patients would receive inpatient medically assisted withdrawal.

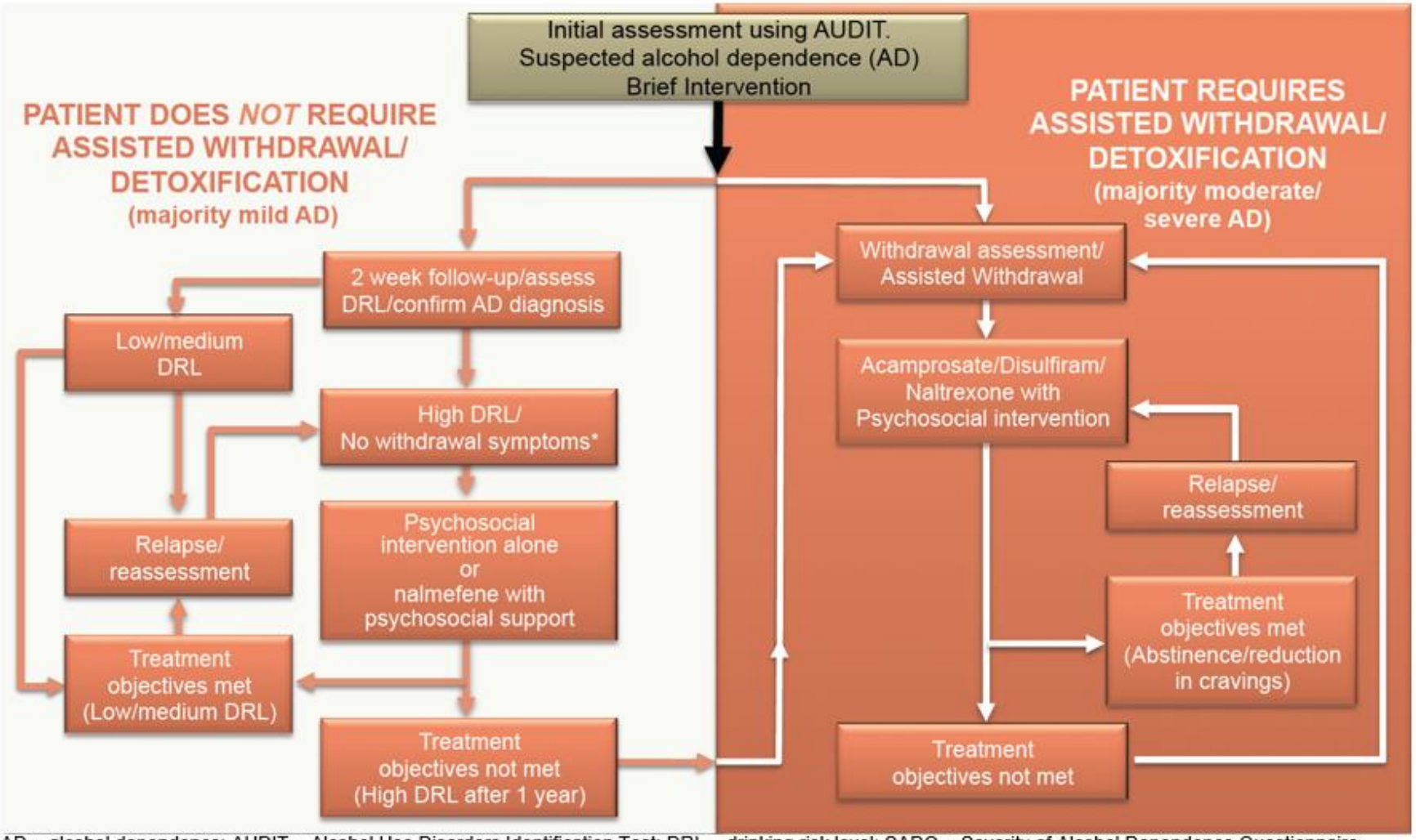
The intensity of PI, in terms of number of sessions and duration of each session is not explicitly stated in the diagrammatic representations provided by the manufacturer. This intensity could have a marked impact on the cost-effectiveness of nalmefene and is discussed further in Chapter 5.

Figure 3: The manufacturer's diagram of current service provision



AD = alcohol dependence; AUDIT = Alcohol Use Disorders Identification Test; SADQ = Severity of Alcohol Dependence Questionnaire.

Figure 4: The manufacturer's anticipated service provision should nalmefene receive a positive recommendation



AD = alcohol dependence; AUDIT = Alcohol Use Disorders Identification Test; DRL = drinking risk level; SADQ = Severity of Alcohol Dependence Questionnaire.
* If there are withdrawal symptoms, withdrawal assessment is required.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem addressed by the MS is reproduced (with minor changes) in Table 2.

Table 2: Decision problem as issued by NICE and addressed by the MS

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with mild alcohol dependence (as defined in NICE CG115) who have a high drinking risk level (≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification	Adults with mild alcohol dependence who have a high drinking risk level without physical withdrawal symptoms, do not require immediate detoxification, and continue to have a high drinking risk level 2 weeks after initial assessment	N/A
Intervention	Nalmefene in conjunction with PI (as defined in NICE CG115)	Nalmefene in conjunction with PI	N/A
Comparator(s)	• PI such as cognitive behavioural therapies, behavioural therapies, or social network and environment-based therapies (as defined in NICE CG115) • Naltrexone (in conjunction with PI as defined in NICE CG115)	PI such as cognitive behavioural therapies, behavioural therapies, or social network and environment-based therapies	In line with the scope for this technology, Lundbeck has considered naltrexone as a relevant comparator when preparing this submission. However, as demonstrated in reviews conducted by NICE (NICE, 2011a) and Lundbeck (see Sections 2.7 and 6.7 of the MS), there is a lack of data on the efficacy of naltrexone in the particular group of patients for which nalmefene is licensed. There are no head-to-head clinical trial data comparing nalmefene and naltrexone directly. Additionally as reported in Sections

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
			2.7 and 6.7 of the MS, it was not possible to conduct an indirect treatment comparison due to lack in reported data in the clinical trials of the efficacy of naltrexone in the particular group of patients for which nalmefene is licensed. However, the use of naltrexone in some patients in the treatment of alcohol dependence has been acknowledged when modelling the treatment sequence.
Outcomes	The outcome measures to be considered include alcohol consumption, alcohol dependence symptoms, compliance/concordance with treatment; objective measures of alcohol consumption; hospitalisations; controlled drinking, change in number of heavy drinking days, morbidity, mortality, adverse effects of treatment, and health-related quality of life.	Outcomes measures considered in the submission include alcohol consumption, alcohol dependence symptoms, proportion of responders, adherence to medication, liver function and other clinical safety laboratory tests (GGT, ALAT, MCV, %CDT), change in number of heavy drinking days, adverse effects of treatment, and health-related quality of life.	N/A
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. The reference case stipulates that the time horizon for estimating clinical effectiveness and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the	The submission will be in line with the final scope. A cost-effectiveness assessment aligned with the reference case presenting cost/QALYs is included. The model also provides outcomes in terms of alcohol-attributable hospitalisations, criminal justice encounters, and	N/A

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	technologies being compared. Costs in the reference case will be considered from an NHS and Personal Social Services perspective. If evidence allows, sensitivity analyses should be presented; analyses should take into account the wider impacts of alcohol dependence (i.e., social and crime issues, including impacts on domestic violence and prisons; social effects of alcohol dependence of adults on children; and the effects of driving while under the influence of alcohol).	mortality.	
Subgroups to be considered	N/A	N/A	N/A
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation.	Evidence is presented for the population and indication covered by the marketing authorisation.	N/A
ALAT, alanine aminotransferase; CDT, carbohydrate-deficient transferrin; GGT, gamma-glutamyl transferase; MCV, mean corpuscular volume; N/A, not applicable; QALY, quality adjusted life year			

3.1 Population

The manufacturer's statement of the decision problem defines the population in line with the final scope as adults with mild alcohol dependence who have a high drinking risk level without physical withdrawal symptoms and who do not require immediate detoxification. However, the MS does not include any details on the mean age at diagnosis of the UK alcohol dependent population (against which to compare the characteristics of people in the clinical trials).

3.2 Intervention

Nalmefene (Selincro, Lundbeck Limited) is an opioid receptor modulator, which exhibits antagonist activity at μ and δ opioid receptors, and partial agonist at κ opioid receptors.

Nalmefene has a UK marketing authorisation for the reduction of alcohol consumption in adults with alcohol dependence who have a high drinking risk level (alcohol consumption more than 60g/day [7.5 units/day] in men and more than 40g/day [5 units/day] in women), without physical withdrawal symptoms and who do not require immediate detoxification. It should only be prescribed in conjunction with continuous PI focused on treatment adherence and reducing alcohol consumption and should be initiated only in people who continue to have a high-risk drinking level two weeks after initial assessment.[14]

Nalmefene is available as an 18mg tablet (corresponding to 20 mg nalmefene hydrochloride and 18.06 mg nalmefene as base),[15] which is taken orally, as needed. The recommended dose is one tablet on each day the person perceives a risk of drinking alcohol, preferably 1-2 hours prior to the anticipated time of drinking. The maximum dosage is one tablet per day.[14]

Nalmefene is available in 14- or 28-tablet packs; the acquisition costs are £42.42 and £84.84, respectively.[16] Nalmefene is contraindicated in the following groups of people: those currently taking opioid analgesics; those with a current or recent opioid addiction; those with acute symptoms of opioid withdrawal; those in whom recent use of opioids is suspected; those with severe hepatic or renal impairment; or those with a recent history of acute alcohol withdrawal.[14] Nalmefene can be prescribed to those with mild or moderate renal impairment but caution should be exercised, for example with more frequent monitoring.[14]

3.3 Comparators

The decision problem addressed in the MS states that the standard comparators considered were (1) PI alone and (2) naltrexone in conjunction with PI. The ERG agrees that these interventions are appropriate and relevant comparators for all adult patients with mild alcohol dependence (without physical withdrawal symptoms and who do not require immediate detoxification); however, some points need further clarification.

NICE CG115[3] recommends that moderation of drinking, rather than abstinence from alcohol, may be appropriate for people with harmful drinking or mild dependence, without significant co-morbidity, and with adequate social support. The usual first-line treatment option in mild alcohol dependence is PI, as detailed in the guideline with pharmacotherapy such as acamprosate or naltrexone added in only when a person with mild alcohol dependence has not responded to PI alone, or has specifically requested pharmacological treatment. It is noteworthy that despite these recommendations (which were based on limited direct evidence for naltrexone in this population and indirect evidence for acamprosate in a population with more severe dependence),[3] oral naltrexone and acamprosate do not have a current UK marketing authorisation for use for the reduction of alcohol consumption as

opposed to abstinence in non-dependent people or people with mild alcohol dependence (p47 of the MS).

3.4 Outcomes

The NICE scope outlines eleven clinical outcome measures and one measure of cost-effectiveness. Most of these are stated to have been addressed in the MS (p58). Clinical outcome measures included alcohol consumption, alcohol dependence symptoms, proportion of responders, adherence to medication, liver function and other clinical safety laboratory tests, change in number of heavy drinking days, adverse effects of treatment, and health-related quality of life (HRQoL). As noted in the MS (p143), these measures were in accordance with the recommendations in the European Medicines Agency (EMA) guideline on the development of medicinal products for the treatment of alcohol dependence for studies addressing the intermediate goal of harm reduction.[17]

Incremental cost per quality adjusted life years (QALYs) gained was used as a measure of cost-effectiveness, which is in accordance with the NICE reference case.[18] The health economic model also provides an account of the wider impacts of alcohol dependence on alcohol attributable hospitalisations, crime and justice, and mortality.

3.5 Other relevant factors

The manufacturer declared that no equity issues were identified (p53 of the MS). The manufacturer identified potential gains from a wider societal perspective (p54-56 of the MS) and evaluated the impact of including a subset of these in sensitivity analyses. The manufacturer made no comment regarding whether NICE's end-of-life criteria were met.

4 CLINICAL EFFECTIVENESS

This chapter presents a review of evidence relating to the clinical effectiveness of nalmefene in addition to PI for the reduction of alcohol consumption in people with alcohol dependence. Section 4.1 presents a critique of the manufacturer's systematic review and Section 4.2 provides a summary of the clinical effectiveness results (efficacy and safety) and critique of included nalmefene trials. Section 4.3 provides an overview and critique of the evidence base considered for establishing relative effectiveness whilst Section 4.4 assesses the quality of any indirect comparison or mixed treatment comparison conducted. Section 4.5 presents additional work on clinical effectiveness undertaken by the ERG and finally, Section 4.6 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The searches undertaken by the manufacturer to identify all relevant pharmacological intervention studies (nalmefene and naltrexone) were conducted in September 2013. The search strategy utilised terms to identify the condition (alcohol dependence), the interventions (nalmefene and naltrexone) and the type of evidence (RCTs and prospective studies). No date or language restrictions were applied. Several electronic bibliographic databases (MEDLINE, MEDLINE in Process, EMBASE, Cochrane Library and PsycINFO) and research registers (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform Search Portal [WHOCTRP], and the International Standard Randomised Controlled Trial Number Register [ISRCTN]) were searched. Supplementary searches such as scanning of bibliographies of included studies and existing systematic reviews were also undertaken. Although the Web of Science Conference Proceedings Index was not searched, Proceedings from the Australasian Professional Society on Alcohol and other Drugs and the International Network on Brief Interventions for Alcohol were reviewed for relevant abstracts presented at meetings held in 2011 and 2012.

The number of hits following a repeat of the MEDLINE search strategy via the PubMed platform for the identification of pharmacological intervention studies on the 16th March 2014 (Section 6.1 of the MS) by the ERG, show numbers to be consistent with those reported in the MS. An updated search in PubMed by the ERG resulted in a further 28 records since September 2013. The ERG has reviewed the records and none was relevant. Whilst the ERG believes that searching additional sources for ongoing and completed trials in Clinicaltrials.gov, WHOCTRP and ISRCTN was appropriate, the terms that were used in these searches were not provided in the MS. As a result, the adequacy of the searches is unclear.

The searches undertaken by the manufacturer to identify all relevant PI studies were conducted in December 2013. As per the pharmacological intervention searches the same data sources were used;

however, searches were restricted by date to 2009 onwards (the purpose of the PI review was to update an existing review of psychosocial comparators that was conducted for NICE CG115)[3] and English language. The number of hits following a repeat of the PubMed search strategy for the identification of PI studies on 26 March 2014 (Table 10.5 of the MS) by the ERG, show numbers to be consistent with those reported in the MS. An update of the search in PubMed by the ERG resulted in a further 133 records since December 2013. The ERG has reviewed the records and found no additional studies since the MS searches.

The ERG considers that the strategy for the pharmacological interventions is comprehensive and that no published studies are likely to have been missed. Although the PI search strategy is comprehensive, restricting by English language can lead to publication bias. Following a clarification request, the manufacturer re-screened all identified PI citations without language restrictions and provided appropriate reasons for exclusion. How this was undertaken by the manufacturer is unclear because the clarification response suggests that not all database searches were re-run without language restrictions.

4.1.2 Inclusion criteria

The MS describes an appropriate method of identifying and screening references for inclusion in the systematic review of nalmefene for the reduction of alcohol consumption in people with alcohol dependence. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any differences in selection were resolved through discussion with a third reviewer (p285, MS). A summary of the inclusion and exclusion criteria, as reported in the MS (p62-63, 286; data re-tabulated in a consistent and more transparent format), for the systematic review of nalmefene is summarised in Table 3.

Table 3: Inclusion/exclusion criteria used to select studies of nalmefene in the MS

	Inclusion criteria	Exclusion criteria
Population	• Adults (≥ 18 years) with alcohol dependency	• Children (aged < 18 years) • Patients who are abstinent or not actively drinking • Patients with a comorbid disorder in addition to the diagnosis of alcohol dependence (e.g. schizophrenia or bipolar disorder) • Patients with co-addiction along with alcohol dependency (e.g. cocaine co-dependence or pathologic gambling)
Intervention	• Treatment with oral nalmefene 20 mg as-needed in conjunction with any type of PI	• Nalmefene used at a dose other than 20 mg • Nalmefene not used as-needed
Comparator	• Nalmefene [a] in conjunction with any type of PI • Placebo in conjunction with any type of PI or best supportive care	• None specified
Outcomes[b]	• Studies reporting endpoints of level and/or pattern of alcohol consumption	• None specified
Study design	• Prospective randomised controlled trials • Non- randomised controlled trials • Long-term follow-up studies • Prospective/retrospective cohort studies and longitudinal studies • Case-control studies • Cross-sectional studies • Systematic reviews and meta-analyses	• Preclinical studies • Phase 1 studies • Non-comparative phase 2 trials • Prognostic studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Non-systematic reviews • Genetic studies • Studies that do not state the level of alcohol consumption of the population in the study • Studies that had a detoxification or alcohol-withdrawal process period before randomisation • Studies only reported as abstract/poster

PI, psychosocial intervention
[a] Possible typographical error. The ERG assumes that this should be naltrexone instead of nalmefene (Table B2, p63, MS)
[b] Note that endpoints of level of alcohol consumption may be reported as secondary endpoints, with the primary endpoint being an "abstinence" endpoint (e.g. relapse to heavy drinking), but the included studies show that the patients were actively drinking at baseline.

The inclusion/exclusion criteria appear to be (mostly) appropriate (and narrowly defined); however, there appears to be some irregularities in the MS.

The manufacturer's systematic review specifically excluded studies that included alcohol dependent people with a co-morbid psychiatric disorder (e.g. schizophrenia or bipolar disorder) or a co-addiction (e.g. cocaine co-dependency or pathologic gambling). Despite the MS (p142) suggesting that many alcohol-dependent patients have diagnosed medical conditions and/or psychiatric co-morbidities, the MS does not provide a reason or rationale for this exclusion. In general, if there is uncertainty in whether there are important differences in effects among various subgroups of people, it may be best to include all of the relevant subgroups and then examine the important and plausible differences in effect in the data analysis. Ideally, this should be planned a priori, and not driven by the availability of data.[19] Furthermore there is a risk that the selected patients may not be representative of those seen in clinical practice.

The manufacturer's systematic review also excluded studies only reported as abstracts or posters; however, no reason or rationale for this exclusion was provided. In order to avoid publication bias, a systematic review should aim to include all relevant studies, regardless of publication status. Although differences often occur between data reported in conference abstracts and their corresponding full reports, differences in results are usually not very large.[20] In addition, it can be difficult to appraise study quality from limited details provided in an abstract. As a result, sensitivity analyses may be carried out to examine the effect of including data from conference abstracts.[21]

The manufacturer's inclusion criterion strictly specifies the intervention as 20mg oral nalmefene, as needed, in conjunction with any type of PI (Table B2, p63, MS). However, all the included studies used 18mg oral nalmefene, as needed, with PI (Table B3, p66, MS). Despite this minor discrepancy, further clarification of the licensed 'nalmefene dose' would have been useful. For example, 18.06 mg oral nalmefene is equivalent to 20 mg nalmefene hydrochloride.[15]

Finally, the statement of the decision problem proposes that the standard comparators to consider include PI alone or naltrexone in conjunction with PI. Whilst the former comparator was considered in the nalmefene systematic review, it is not clear whether the latter was considered (see Table 2) due to a possible typographical error in Table B2 of the MS (p63). However, the ERG believes that the MS has appropriately considered naltrexone in conjunction with PI as a comparator in the nalmefene systematic review.

4.1.3 Critique of data extraction

The data extracted and presented in the MS clinical section appear appropriate and comprehensive.
As noted in the manufacturer's response to clarification question B1, data extraction was performed by one researcher and checked by a second.

4.1.4 Quality assessment

The validity assessment tool used to appraise the included studies in the MS (p91) was based on the quality assessment criteria for RCTs, as suggested by the NICE guideline template for manufacturers.[22] As noted in the manufacturer's response to clarification question B1, methodological quality assessment of included studies was performed by one researcher and checked by a second. The ERG acknowledges that the validity assessment tool used in the manufacturer's submission was appropriate.

4.1.5 Evidence synthesis

The MS adequately reported the statistical analyses in the ESENSE1, ESENSE2 and SENSE trials (p82-86, MS); however, a conventional pairwise meta-analysis of the three studies was not undertaken (p106, MS). The MS states that "…individual patient data… from ESENSE1 and ESENSE2 were pooled to analyse outcomes on the primary and secondary endpoints. Data from all three RCTs were pooled to analyse safety outcomes." No further details on the methods of pooling were provided in the MS. After seeking further clarification (questions B7 and B10) the manufacturer indicated that a pooled effect analysis was done on patient level data and therefore the within-study variability can be considered as adequately handled. In addition, a country adjustment was performed when pooling clinical data and was deemed more accurate than an adjustment on study because of being more reliable to handle the between-study variability (the ERG notes that it is not clear whether there was an investigation of a country by treatment interaction).[23-25] Despite this, the manufacturer provided a meta-analysis of the three nalmefene studies as requested by the ERG; however, the meta-analytical methods of synthesis were not reported.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in/excluded from the submission

The manufacturer's PRISMA (formerly QUORUM) flow diagram relating to the literature searches does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/statement.htm). Despite this, the flow diagram (p65; MS) appears to be an adequate record of the literature searching and screening process for nalmefene studies. Moreover, although the MS initially failed to provide a full and explicit breakdown of the reasons why each citation was rejected (especially after full text papers were retrieved for detailed evaluation), further details were provided by the manufacturer in their response to clarification question B2 and B3. Of the 291 full text screened papers that were excluded, detailed reasons for exclusion were only provided for 276 records. It is unclear to the ERG why the remaining full text studies were excluded.

As noted in the MS (p29, 64, 277-278) five studies that were part of the development programme for nalmefene in alcohol use disorders (funded by Biotie Therapies Corporation) were excluded. According to the inclusion/exclusion criteria of the manufacturers systematic review, three of these studies were excluded due to the following reasons: one study included people who were required to be abstinent prior to treatment (CPH-101-0299);[26] one study used a fixed un-licensed daily dose (CPH-101-0400, unpublished) and one study had no relevant comparator group (CPH-101-399 unpublished). Study CPH-101-701 (unpublished; n=166) and study CPH-101-0801 (n=403)[27] were randomised, double-blind, placebo-controlled, alongside biopsychosocial assessment feedback and advice, 28 week studies, using a flexible dose regime (10, 20, 40mg of nalmefene hydrochloride) as needed in patients with alcohol dependence or other alcohol use disorders.[15] Study CPH-101-701 was conducted at multi-sites in the UK whereas study CPH-101-0801 was conducted at multi-sites in Finland. Although no rules were pre- specified for dealing with studies that only partially addressed the population of interest in the manufacturer's systematic review, study CPH-101-801 was excluded as 7% of the study population did not meet the criteria for alcohol dependence (93% were alcohol dependent). Study CPH-101-0701 was also excluded on a similar basis ([redacted]). In addition, both studies used flexible dosing regimens for nalmefene. As noted in the manufacturer's clarification response to question B3, the design and context of these studies were not aligned with the licensed indication for nalmefene.[15]

- Main evidence (pivotal studies)

No head-to-head RCTs comparing nalmefene plus PI with naltrexone plus PI were identified in the manufacturer's systematic review. In the absence of head-to-head studies, the MS included three manufacturer sponsored RCTs that compared the use of nalmefene plus PI with placebo plus PI: ESENSE1 (12014A; NCT00811720), ESENSE2 (12023A; NCT00812461) and SENSE (12013A; NCT00811941) as the main supporting evidence for the efficacy and safety of oral nalmefene for the reduction of alcohol consumption in people with presumed mild alcohol dependence (given that no confirmation of diagnosis severity was undertaken using a measure such as the SADQ score in these studies). A summary of the study design and population characteristics of the three trials is provided in Table 4.

Table 4: Characteristics of included studies

Study	Country (sites)	Design	Population	Interventions	Comparator	Primary outcome measures	Duration
ESENSE1 (Study 12014A)[28-30]	Austria (n=4), Finland (n=11), Germany (n=16), and Sweden (n=8)	Phase III randomised, double-blind, placebo-controlled, parallel-group trial (n=604)	Patients aged ≥ 18 years (recruited from in- and out- patient clinics) with a primary diagnosis of alcohol dependence according to DSM-IV-TR criteria; ≥ 6 HDDs, an average alcohol consumption at WHO medium risk level or above or ≤ 14 abstinent days in the 4 weeks preceding the screening visit	Oral nalmefene 18 mg (fixed daily dose tablet, as-needed use) plus PI [a] (n=306)	Placebo (matching tablet, as-needed use) plus PI [a] (n=298)	Change from baseline in the monthly number of heavy drinking days[b] and total alcohol consumption (g/day)[c] at month 6.	6 months

ESENSE2 (Study 12023A)[29,31,32]	Belgium (n=7), Czech Republic (n=3), France (n=16), Italy (n=10), Poland (n=7), Portugal (n=4), and Spain (n=10	Phase III randomised, double-blind, placebo-controlled, parallel-group trial (n=718)	Patients aged ≥ 18 years (recruited from in- and out- patient clinics) with a primary diagnosis of alcohol dependence according to DSM-IV-TR criteria; ≥ 6 HDDs, an average alcohol consumption at WHO medium risk level or above or ≤ 14 abstinent days in the 4 weeks preceding the screening visit	Oral nalmefene 18 mg (fixed daily dose tablet, as-needed use) plus PI [a] (n=358)	Placebo (matching tablet, as-needed use) plus PI [a] (n=360)	Change from baseline in the monthly number of heavy drinking days[b] and total alcohol consumption (g/day)[c] at month 6.	6 months
SENSE (Study 12013A)[32-34]	Czech Republic (n=5), Estonia (n=5), Hungary (n=2), Latvia (n=4), Lithuania (n=2), Poland (n=15), Russia (n=8), Slovakia (n=4),	Phase III, randomised, double-blind, placebo-controlled, parallel-group trial (n= 675)	Patients aged ≥ 18 years (recruited from outpatient clinics) with a primary diagnosis of alcohol dependence according to DSM-IV-TR criteria; ≥ 6 an average alcohol consumption at low risk level or above or	Oral nalmefene 18 mg (fixed daily dose tablet, as needed use) plus PI [a] (n=509)	Placebo (matching tablet, as-needed use) plus PI[a] (n=166)	Long-term safety and tolerability (adverse events, clinical safety laboratory tests and vital signs) Change from baseline in the monthly number of heavy drinking days[b] and total alcohol	52 weeks

	Ukraine (n=10), and the UK (n=5)		≤ 14 abstinent days in the 4 weeks preceding the screening visit			consumption (g/day)[c] at month 6.	

DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; HDD, heavy drinking days; PI, psychosocial intervention

[a] Psychosocial support provided as a motivational and adherence enhancing intervention (BRENDA) to support change in behaviour and improve adherence to treatment. This was delivered at weekly intervals for the first 2 weeks and monthly thereafter (sessions limited to approximately 15-30 minutes except for the first session [administered at randomisation] which was approximately 30-40 minutes).

[b] Defined as a day with alcohol consumption ≥ 60 g for men and ≥ 40 g for women.

[c] Defined as mean daily alcohol consumption in g/day over a month (28 days).

ESENSE1 and ESENSE2 trials (p60-105, MS)

The ESENSE1 (n=604)[28] and ESENSE2 (n=718)[31] trials were published, 24 week, randomised, double-blind, multinational (excluding UK), multicentre, parallel-group, placebo-controlled European phase III trials, designed to determine the efficacy of oral nalmefene in men and women (aged 18 years or over) with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) diagnosis of alcohol dependence and at least six heavy drinking days in the preceding 28 days. A heavy drinking day was defined as ≥60 g/day for men and ≥40 g/day for women. In addition, people had an average daily alcohol consumption level conferring medium risk or higher (defined as ≥40g/day for men and ≥20g/day for women) or ≤ 14 abstinent days in the 4 weeks preceding the screening visit. In both studies, individuals with a history of delirium tremens, withdrawal symptoms requiring medication (a Revised Clinical Institute Withdrawal Assessment for Alcohol Score ≥10), liver function abnormalities (aspartate aminotransferase and/or alanine aminotransferase >3 times the upper reference limit), blood alcohol concentration >0.02% and severe medical conditions or psychiatric comorbidities at screening or randomisation were excluded.

The ESENSE1 and ESENSE2 trials consisted of four sequential periods. Both studies began with a one to two week screening period, after which patients were randomised 1:1 to 24 weeks of as-needed treatment with 18 mg nalmefene plus PI or placebo plus PI. Participants were instructed to take one tablet on each day they perceived a risk of drinking alcohol, preferably 1-2 hours before drinking (with a maximum of one tablet per day). If the patient started drinking without having taken a tablet, they were advised to take one tablet as soon as possible. The patients who completed 24 weeks of double-blind treatment entered a four week, double-blind run-out period (to evaluate any treatment discontinuation effects). The patients initially randomised to nalmefene were re-randomised 1:1 to receive nalmefene or placebo, and the patients initially randomised to placebo continued on placebo; re-randomisation was done concurrently with the initial randomisation. Finally, a safety follow-up visit was scheduled for four weeks after completion of the run-out period or after withdrawal from the study.

In both studies, patients in the treatment and placebo groups received motivational and adherence-enhancing PI sessions (termed BRENDA) which included the following six components: (1) a biopsychosocial evaluation, (2) a report of findings from the evaluation given to the patient, (3) empathy, (4) addressing patient needs, (5) providing direct advice, and (6) assessing patient reaction to advice and adjusting the treatment plan as needed. All PI sessions were provided by trained personnel (e.g. the investigators, nurses and psychologists) and were delivered at weekly intervals for the first 2 weeks and monthly thereafter. Sessions were limited to approximately 15-30 minutes except for the first session, which was administered at randomisation and lasted

approximately 30-40 minutes. No treatment goal was defined, that is both abstinence and reduction of alcohol intake were accepted and no information was collected on individual treatment goals.

The co-primary outcome measures for the ESENSE studies were the changes from baseline in the number of heavy drinking days per month, and total alcohol consumption in g/day at month six. Patients self-reported their daily alcohol consumption using the timeline follow-back method to estimate retrospectively the number of standard drinks each day (defined as a 24-hour period starting at 6am to 6am the following morning). Although this method of assessment has limitations due to its subjectiveness, the MS (p78) notes that the timeline follow-back method is widely used in alcohol clinical trials for alcohol dependence and gives reliable retrospective self-reports of drinking in outpatients.[35-38]

In the 1−2 weeks between screening and randomisation, a large proportion of people reduced their alcohol intake to less than six heavy drinking days per month or below a medium drinking risk level (18% [102/579, full analysis set] in ESENSE1[28] and 33% [218/655, full analysis set] in ESENSE2)[31] and so no longer fulfilled the pre-specified inclusion criteria. As a result, any further benefits in terms of reduction in alcohol intake that could be gained from treatment were limited in these people. In addition, during the main treatment period after randomisation, approximately 40% of people withdrew from each study (in ESENSE1, 53% [160/302] for nalmefene-treated participants and 31% [91/296] for placebo treated participants and in ESENSE2, 41% [140/341] for nalmefene treated participants and 38% [127/337] for placebo-treated participants) leading to missing data, which may have affected the statistical analyses. As described later the manufacturer used multiple imputation methods to address this issue.

To address these issues, the manufacturer performed a post-hoc subgroup analyses to assess the benefits of nalmefene and establish the population that would benefit most from treatment. The post-hoc subgroup efficacy analyses included participants from ESENSE1 (n=338) and ESENSE2 (n=303) who maintained a high or very high drinking risk level (alcohol consumption ≥60 g/day [≥7.5 units/day] for men and ≥40 g/day [≥5 units/day] for women) between screening and randomisation. The subsequent marketing authorisation was granted for this subgroup of people only.[15]

SENSE trial (p60-105, 142, MS)

The SENSE (n=675) trial was a 52 week, randomised, double-blind, multinational (including the UK), multicentre, parallel-group, placebo-controlled European phase III trial.[32,34] It was primarily designed to collect long-term safety data on nalmefene, however, after study initiation, a protocol amendment was made to include efficacy analyses at month six. Participants included

men and women (aged over 18 years) with a DSM-IV-TR diagnosis of alcohol dependence and at least six heavy drinking days in the preceding 28 days. The people included had an average daily alcohol consumption level conferring low risk or higher or ≤ 14 abstinent days in the 4 weeks preceding the screening visit. Individuals with a history of delirium tremens, withdrawal symptoms requiring medication (a Revised Clinical Institute Withdrawal Assessment for Alcohol Score ≥10), liver function abnormalities (aspartate aminotransferase and/or alanine aminotransferase >3 times the upper reference limit), blood alcohol concentration >0.02% and severe medical conditions were excluded; however, people with psychiatric comorbidities such as depression, anxiety, social phobia and insomnia, were included.

Similar to the ESENSE studies, the SENSE trial had an initial 1- to 2-week screening period, after which patients were randomised 3:1 to 52 weeks of as-needed treatment with nalmefene plus PI or placebo plus PI. A safety follow-up visit was scheduled for 4 weeks after completion of the study or after withdrawal from the study. All PI sessions (BRENDA) were provided by trained personnel and were delivered at weekly intervals for the first 2 weeks and monthly thereafter. The co-primary outcome measures included: long-term safety and tolerability and changes from baseline in the number of heavy drinking days per month and total alcohol consumption at month six. In the 1−2 weeks between screening and randomisation, a large proportion of people reduced their alcohol intake to less than six heavy drinking days per month or below a medium drinking risk level (39% [215/552, full analysis set] and no longer fulfilled the pre-specified inclusion criteria.[34] In addition, during the main treatment period after randomisation, 37% (243/665) of people withdrew from the study (38% [191/501] and 32% [52/164] for nalmefene-treated and placebo-treated participants, respectively)[34] leading to missing data, which may have affected the statistical analyses. As described later the manufacturer used multiple imputation methods to address this issue. The post-hoc subgroup efficacy analyses, as per the licensed population, included 183 participants (full analysis set) who had a high or very high drinking risk level at both screening and randomisation.

- *Ongoing studies of nalmefene (p32, MS)*

Several ongoing studies were noted in the MS; however, detailed study characteristics (including expected completion dates) were lacking. A summary of relevant studies, as reported in the MS (p32), for the use of nalmefene in people with alcohol dependence is summarised in Table 5.

Table 5: List of ongoing studies

Ongoing/ planned study	Design	Objective	Duration and planned recruitment	Expected start
1	Non-interventional, multinational, prospective cohort study	To provide data related to the patterns of use and of the frequency of selected adverse events in the overall treated population and in subpopulations in routine clinical practice	An 18-month post-authorisation safety study (PASS). Planned recruitment not reported.	Not reported; however, This study will commence in each country only after nalmefene has been launched in that country. Information about the study progress will be registered on the EU PASS register ENCEPP/SDPP/5678).
2	Non-interventional prospective longitudinal cohort study of patients with alcohol dependence at treatment initiation and followed by occupational healthcare physicians up to 12 months in Finland.	The primary objectives are to describe the evolution of alcohol consumption and sick leave days registered by the physician in patients with alcohol dependence initiating treatment, overall and by type of treatment, after 6 months of treatment and to identify the factors associated with the evolution of sick leave days registered by the physician after 6 months of treatment.	This study is planned to last 6 months to assess the primary objective, but patients will be followed until 12 months to obtain long-term data. Planned recruitment not reported.	The first patient's first visit was performed in Q4 2013.
3	Exploratory,	To determine the use of	A 12-week study	The first patient's first

	interventional, open-label, fixed-dose study conducted in Germany	fixed-dose nalmefene (as-needed) in alcohol-dependent patients with liver impairment. Main exploratory endpoints are reduction in alcohol consumption and change in liver stiffness.	that will recruit 60 subjects.	visit is expected in Q3 2014. Recruitment period is 6 months.
4	Interventional, open-label study of 18 mg nalmefene as-needed use in the treatment of patients with alcohol dependence in primary care across 5 European countries (planned).	The primary objective is to determine the reduction in alcohol consumption of nalmefene in conjunction with continuous psychosocial support in primary care	A 12-week study that will recruit 635 subjects.	The first subject is expected in Q3 2014. Recruitment period is 12 months.

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that all relevant studies were included in the MS and details of ongoing trials that are likely to be reporting additional evidence within 12 months were reported.

4.2.3 Summary and critique of manufacturer's analysis of validity assessment

The manufacturer provided a formal appraisal of the validity of the included nalmefene RCTs using standard and appropriate criteria. The completed validity assessment tool for the three pivotal trials, as reported in the MS, is reproduced in Table 6.

Table 6: Quality assessment results for RCTs included by the manufacturer (p91, MS)

Quality assessment criteria	Trials		
	ESENSE1 (Study 12014A)	ESENSE2 (Study 12023A)	SENSE (Study 12013A)
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No[a]	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes[b]	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes[c]	Yes[c]	Yes[c]

[a] Data discrepancy - the MS (Appendix 5, Table 10-17, p298-299) also suggest that this criteria was met

[b] Data discrepancy - the MS (Appendix 5, Table 10-17, p298-299) also suggest that this criteria was not met

[c] Modified intention to treat analysis (manufacturer's clarification response to question B14) which corresponds to all randomised patients excluding those who did not take the treatment or all investigational medicinal product returned.

The MS states that in the ESENSE1,[28-30] ESENSE2[29,31,32] and SENSE[32-34] trials, randomisation (in blocks of 4) was performed according to a computer generated randomisation list, allocation concealment was done using sealed envelopes (the opaqueness of envelopes was not reported in all studies) and participants and investigators were blinded to treatment allocation (double-blind). The ERG acknowledges that adequate methods of randomisation, allocation concealment and blinding were used in the conduct of included trials.

As individual patient data were available to the manufacturer (p106, MS) it is unclear whether or not they formally looked for statistically significant differences between treatment groups at baseline.

Nevertheless, the primary published papers[28,29,31] and the MS suggest (p298-301) that no clinically relevant differences in baseline demographic or clinical characteristics were observed across the treatment groups between the ESENSE1 and ESENSE2 trials (total population and licensed population). In the SENSE study, notable differences were only observed between treatment groups of the licensed population in the proportion of patients with a family history of alcohol-related problems (nalmefene plus PI, 50.3% [73/145] versus placebo plus PI, 35.7% [15/42]) and the proportion of patients who had previously been treated for alcohol dependence (nalmefene plus PI, 22.1% [32/145] versus placebo plus PI, 31.0% [13/42]).

Whilst all study withdrawals were adequately described and all patients were accounted for, approximately 40% of the total population withdrew during the main treatment period from each study (ESENSE1, ESENSE2 and SENSE) after randomisation. In general, the validity of a study may be threatened if attrition is more than 20%.[39] Moreover, the subgroup analysis i.e. the basis of the licensed population, of the ESENSE1 and ESENSE2 trials was not pre-specified, thus the size of the subgroups could lack statistical power. However, a scientific advisory group, which was consulted by the regulatory authority, recognised the validity of the post-hoc analysis defining the target population and acknowledged that whilst post-hoc analyses are not ideal, they are commonly used in clinical trials for psychiatric drugs, given the high dropout rates encountered with these populations.[15] In addition, sensitivity analyses were undertaken by the manufacturer to examine the impact of missing data due to the high withdrawal rates using a range of imputation methods (baseline observation carried forward; last observation carried forward; multiple imputation; mixed model repeated measures; observed cases and placebo mean imputation). For further details refer to p140-142 of the MS.

Ideally in an intention to treat (ITT) analysis participants should be analysed in the groups to which they were randomised regardless of which (or how much) treatment they actually received, and regardless of other protocol irregularities such as noncompliance, protocol deviations and withdrawals. Although the post-randomisation inclusions were pre-specified, the ERG acknowledges that the removal of ineligible patients (i.e. participants without recorded intervention intake and/or having at least one valid post baseline assessment of alcohol consumption) from both study arms who received treatment after randomisation is acceptable (i.e. modified ITT analysis) and will lead to an unbiased assessment of treatment effect in patients who do meet the inclusion criteria providing there are not so many patients removed that the protection of the randomisation is lost.[40,41]

4.2.4 Summary and critique of results

This section presents the results, as reported by the manufacturer, of the licensed population (people with a high /very high drinking risk level at baseline and randomisation) from three manufacturer-

sponsored RCTs (ESENSE1, ESENSE2 and SENSE). These data formed the main supporting evidence for the efficacy and safety of nalmefene plus PI in the treatment of people with presumed mild alcohol dependence (no confirmation of diagnosis severity was undertaken using a measure such as the SADQ score in these studies). Additional information, not reported in the MS, was provided by the manufacturer in their response to the clarification questions raised by the ERG. Where applicable, data have been re-tabulated in a consistent and more transparent format by the ERG.

4.2.4.1 Efficacy

The main efficacy endpoints (co-primary outcome measures) in the ESENSE1, ESENSE2 and SENSE trials included changes from baseline in the number of heavy drinking days per month and total alcohol consumption at month six. All analyses were conducted according to the modified intention to treat principle using a mixed model repeated measures approach. The manufacturer's clarification responses to question B9, B11, B12, and B13 note that the mixed model repeated measures analysis uses all available data measured over each month during the treatment period and provides an unbiased estimate of the treatment effect under the assumption that missing data are missing at random. The pooled results using the mixed model repeated measures analysis makes use of more evidence available from each time-point and assumes that the treatment effect is constant across countries. The conventional pairwise meta-analysis allows for heterogeneity in treatment effect between studies but only makes use of evidence available at 6 months. However, with only three studies, estimating the between study standard deviation is difficult using conventional methods and the test for heterogeneity has low power. Therefore, both approaches have their limitations, although the results were consistent.

Heavy drinking days (manufacturer's clarification response to question B7)

In the subgroup of people who continued to have a high or very high drinking risk level at baseline and randomisation (i.e. the licensed population) in the ESENSE1, ESENSE2 and SENSE trials, [redacted]. Additional data from the SENSE trial found that the beneficial effect of nalmefene plus PI was sustained for 52 weeks (-3.6 heavy drinking days per month; 95% CI: -6.5 to -0.7; p=0.0164). The ERG notes that despite uncertainty as to what constitutes a clinically relevant magnitude of reduction of alcohol intake, a scientific advisory group, which was consulted by the EMA during the regulatory process for nalmefene, confirmed (by majority decision) that the beneficial effect size of nalmefene plus PI compared with placebo plus PI in the ESENSE1 and ESENSE2 trials was clinically meaningful and the risk-benefit balance to be

favourable.[15] A detailed summary of the outcomes data for each trial (data) is provided in Appendix 1.

Figure 5: Heavy drinking days (days/month) – conventional pairwise meta-analysis of changes from baseline to Month 6: Licensed population[a]

[redacted]

[redacted]

Table 7: Heavy drinking days (days/month) – pooled analysis (using patient level data adjusted by country) of changes from baseline to Month 6: Licensed population[a]

Treatment Group	Change from baseline to Month 6		Difference to placebo		
	N	Mean ± SE	Mean ± SE	95% CI	p-value
Pooled studies: ESENSE1, ESENSE2, SENSE					
Nalmefene plus PI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo plus PI					

CI, confidence interval; PI, Psychosocial Intervention, [a] Full analysis set using a mixed model repeated measures approach

Total alcohol consumption (manufacturer's clarification response to question B7)

In the subgroup of people who continued to have a high or very high drinking risk level at baseline and randomisation (i.e. licensed population) in the ESENSE1, ESENSE2 and SENSE trials, [redacted] Additional data from the SENSE trial found that the beneficial effect of nalmefene plus PI was sustained for 52 weeks (-17.3g per day total alcohol consumption; 95% CI: -30.9 to -3.8; p=0.0129). A detailed summary of the outcomes data for each trial (data) is provided in Appendix 1.

Figure 6: Total alcohol consumption (g/day) – conventional pairwise meta-analysis of changes from baseline to Month 6: Licensed population[a]

[redacted]

[redacted]

Table 8: Total alcohol consumption (g/day) – pooled analysis (using patient level data adjusted by country) of changes from baseline to Month 6: Licensed population[a]

Treatment Group	Change from baseline to Month 6 (g/day)		Difference to placebo		
	N	Mean ± SE	Mean ± SE	95% CI	p-value
Pooled studies: ESENSE1, ESENSE2, SENSE					
Nalmefene plus PI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo plus PI					

Superseded – see Erratum

CI, confidence interval; PI, Psychosocial Intervention, [a] Full analysis set using a mixed model repeated measures approach

Secondary outcomes

A range of secondary efficacy endpoints were reported in the MS (p94-105) including the following: responder analysis based on various drinking measures (e.g. a downward shift from baseline in WHO drinking risk levels by two risk categories and reduction from baseline in monthly total alcohol consumption); alcohol dependence symptoms and clinical status (change from baseline in Clinical Global Impression –Improvement [clinician assessed] Scale, Clinical Global Impression-Severity Scale and Drinker Inventory of Consequences Score); liver function test results (serum-gamma-glutamyl transferase and serum-alanine amino transferase activities); and quality of life measures (SF-36 and EQ-5D). For some of these outcomes the manufacturer undertook pooled analyses based on individual patient data (measures which included responder analysis, SF-36, EQ-5D and the Drinker Inventory of Consequences total score), whereas for other outcomes data were reported for each individual study. The rationale for the different approaches was not provided. For detailed results refer to p94-105 of the MS and Appendix 4 of the manufacturer's clarification response to question B6.

In brief, pooled post-hoc analyses in the licensed population of the ESENSE1 and ESENSE2 trials found a significantly higher rate of responders with a two-category downward shift from baseline in WHO drinking risk levels (i.e. for patients at very high risk at baseline, response was defined as a shift to medium risk or below; for patients at high risk at baseline, response was defined as a shift to low risk or below) at month 6 in the nalmefene plus PI group compared with the placebo plus PI group. Similarly, in the pooled analysis of the licensed groups of the ESENSE1 and ESENSE2 trials, quality of life assessments using the SF-36 mental and physical component scores, EQ-5D utility index and health state scores and the Drinker Inventory of Consequences total score showed significantly greater improvements with nalmefene plus PI compared with placebo plus PI. A summary of these pooled results is provided in Table 9 (further details are provided in Appendix 2).

Table 9: Summary of the pooled (ESENSE1 and ESENSE2 trials) secondary outcome results at month 6: Licensed population (p95-103, MS)

Secondary outcomes	**Pooled results: ESENSE1 and ESENSE2[a]**		
Responder analysis	**Odds ratio**	**95% CI**	**p-value**
RSDRL (response defined as a downward shift from baseline in DRL by two risk categories)	1.87 [b]	1.35; 2.59	< 0.001
RLDRL (response defined as a downward shift from baseline in DRL to low DRL or lower)	1.79	1.27; 2.53	< 0.001
≥ 70% Reduction in total alcohol consumption	1.88	1.32; 2.70	< 0.001
Quality of life measures	**Mean difference to placebo (±SE)**	**95% CI**	**p-value**
SF-36 mental component score	3.09 ±0.92	1.29; 4.89	0.0008
SF-36 physical component score	1.23 ±0.55	0.15; 2.31	0.0259
EQ-5D utility index score	0.03 ±0.02	0.00; 0.06	0.0445
EQ-5D health state score	3.46 ±1.38	0.75; 6.17	0.0124
Drinker Inventory of Consequences total score –Recent drinking	-3.22 ±1.47	-6.12; -0.33	0.0292

CI, confidence interval; DRL, drinking risk level; SE, standard error; SF-36, SF-36 Health Survey; EQ-5D, EuroQoL-5 Dimensions.
[a] Pooled estimate based on individual patient data: full analysis set using the mixed model repeated measures analysis approach
[b] Pooled estimate including 6 month data from the SENSE trial: Odds Ratio, 1.55; 95%CI: 1.06; 2.25, p=0.0022 (p157, Table B47, MS)

In both the ESENSE1 and ESENSE2 trials (licensed populations) the Clinical Global Impression – Improvement Scale and the Clinical Global Impression-Severity Scale improved significantly with

nalmefene plus PI compared with placebo plus PI. Similarly, there were significantly greater reductions in liver enzyme levels (gamma-glutamyl transferase and serum-alanine amino transferase) with nalmefene plus PI compared with placebo plus PI at 6 months in each study.

4.2.4.2 Safety and tolerability

This section presents the main safety evidence from all participants who received at least one dose of study drug within the ESENSE1, ESENSE2 and SENSE trials. Safety results are presented for both the licensed population and the total population.

In the licensed population of the ESENSE and SENSE trials (p138 of the MS and manufacturer's clarification response to question B19), adherence to the as needed nalmefene dosing regimen (defined as a day when there was alcohol consumption and concomitant nalmefene medication intake or a day when there was no alcohol consumption) was high in each trial (ESENSE1, 75.7%; ESENSE2, 85.1%; SENSE, 86.7% and all trials pooled, 82%). These adherence rates were similar to that observed in the total population of the nalmefene trials (ESENSE1, 78.5%; ESENSE2, 87.2%, SENSE, 92.6% and all trials pooled, 87%).

A summary of the rates of discontinuation (including reasons for premature termination) for all participants within the three trials (licensed population) are presented in Table 10. Although a statistical analysis comparing the rates of study discontinuation between the treatment groups in each study was not reported in the MS, higher rates of patient withdrawal were observed in the nalmefene plus PI group compared with the placebo plus PI group. The main reasons for study discontinuation were withdrawal of consent and adverse events. As noted in the MS (p133-134), treatment emergent adverse events leading to withdrawal occurred in [redacted] patients in the pooled nalmefene plus PI group compared with [redacted] patients in the pooled placebo plus PI group.

In the total population of the ESENSE1, ESENSE2 and SENSE trials, similar rates of study discontinuation were observed to those in the licensed populations. Further details are provided in Table 11. As noted in the MS (p133), treatment emergent adverse events leading to withdrawal in the total population occurred in 149/1144 (13.0%) patients in the pooled nalmefene plus PI group compared with 47/797 (5.9%) patients in the placebo plus PI group.

Table 10: Number (%) of patients discontinuing treatment in the ESENSE1, ESENSE2 and SENSE trials: Licensed population (Data derived from MS, p88-90)

Adverse event	ESENSE1		ESENSE2		SENSE		Pooled	
	Nalmefene + PI	Placebo + PI	Nalmefene + PI	Placebo + PI	Nalmefene + PI	Placebo + PI	Nalmefene + PI	Placebo + PI
Subjects randomised	180	170	155	162	145	42	480	374
Subject s who received treatment	179 (100%)	169 (100%)	152 (100%)	158 (100%)	144 (100%)	42 (100%)	475 (100%)	369 (100%)
Subjects who completed the study	77 (43.0%)[a]	107 (63.3%)	97 (63.8%)	101 (63.9%)	77 (53.5%)	28 (66.7%)	251 (52.8%)	236 (64.0%)
Primary reason for study discontinuation	102 (57.0%) [a]	62 (36.7%)	55 (36.2%)	57 (36.1%)	67 (46.5%)	14 (33.3%)	224 (47.2%)	133 (36.0%)
Adverse event	45 (25.1%)	13 (7.7%)	5 (3.3%)	6 (3.8%)	15 (10.4%)	0	65 (13.7%)	19 (5.1%)
Lack of efficacy	13 (7.3%)	17 (10.1%)	4 (2.6%)	8 (5.1%)	1 (0.7%)	0	18 (3.8%)	25 (6.8%)
Non-compliance	9 (5.0%)	0	1 (0.7%)	2 (1.3%)	3 (2.1%)	1 (2.4%)	13 (2.7%)	3 (0.8%)
Protocol violation	9 (5.0%)	4 (2.4%)	11 (7.2%)	14 (8.9%)	8 (5.6%)	2 (4.8%)	28 (5.9%)	20 (5.4%)
Withdrawal of consent	18 (10.1%)	19 (11.2%)	21 (13.8%)	18 (11.4%)	32 (22.2%)	10 (23.8%)	71 (14.9%)	47 (12.7%)
Lost to follow up	6 (3.4%)	6 (3.6%)	4 (2.6%)	4 (2.5%)	1 (0.7%)	0	11 (2.3%)	10 (2.7%)
Other (not specified)	2 (1.1%)	3 (1.8%)	9 (5.9%)	5 (3.2%)	7 (4.9%)	1 (2.4%)	18 (3.8%)	9 (2.4%)

PI, Psychosocial Intervention, [a] This number differs from that in the MS, which was a typographical error as confirmed in clarification response D1.

Table 11: Number (%) of patients discontinuing treatment in the ESENSE1, ESENSE2 and SENSE trials: Total population (Data derived from EMA assessment report of nalmefene[15] and van den Brink *et al.*[34])

Adverse event	ESENSE1		ESENSE2		SENSE [a]		Pooled	
	Nalmefene + PI	Placebo + PI	Nalmefene + PI	Placebo + PI	Nalmefene + PI	Placebo + PI	Nalmefene + PI	Placebo + PI
Subjects randomised	306	298	358	360	509	166	1173	824
Subject s who received treatment	302 (100%)	296 (100%)	341 (100%)	337 (100%)	501 (100%)	164 (100%)	1144 (100%)	797 (100%)
Subjects who completed the study	142 (47.0%)	205 (69.3%)	201 (58.9%)	210 (62.3%)	310 (61.9%)	112 (68.3%)	653 (57.1%)	527 (66.1%)
Primary reason for study discontinuation	160 (53.0%)	91 (30.7%)	140 (41.1%)	127 (37.7%)	191 (38.1%)	52 (31.7%)	491 (42.9%)	270 (33.9%)
Adverse event	62 (20.5%)	20 (6.8%)	15 (4.4%)	8 (2.4%)	43 (8.6%)	2 (1.2%)	120 (10.5%)	30 (3.8%)
Lack of efficacy	18 (6.0%)	22 (7.4%)	7 (2.1%)	13 (3.9%)	3 (0.6%)	2 (1.2%)	28 (2.4%)	37 (4.6%)
Non-compliance	13 (4.3%)	0	8 (2.3%)	6 (1.8%)	8 (1.6%)	1 (0.6%)	29 (2.5%)	7 (0.9%)
Protocol violation	15 (5.0%)	8 (2.7%)	26 (7.6%)	34 (10.1%)	17 (3.4%)	5 (3.0%)	58 (5.1%)	47 (5.9%)
Withdrawal of consent	34 (11.3%)	28 (9.5%)	52 (15.2%)	43 (12.8%)	94 (18.8%)	35 (21.3%)	180 (15.7%)	106 (13.3%)
Lost to follow up	14 (4.6%)	8 (2.7%)	14 (4.1%)	11 (3.3%)	12 (2.4%)	3 (1.8%)	40 (3.5%)	22 (2.8%)
Other (not specified)	4 (1.3%)	5 (1.7%)	18 (5.3%)	12 (3.6%)	14 (2.8%)	4 (2.4%)	36 (3.1%)	21 (2.6%)

PI, Psychosocial Intervention

In the pooled subgroup of people with at least a high drinking risk level at screening and randomisation (licensed population), 368/475 (77.5%) patients in the nalmefene plus PI group experienced a treatment emergent adverse event compared with 246/369 (66.7%) patients in the placebo plus PI group (p-value not reported). A summary of the most common treatment-related adverse events, as reported by the manufacturer and adapted (data re-tabulated in a consistent and more transparent format) by the ERG is presented in Table 12. The most common treatment-related adverse events in the nalmefene plus PI group were nausea (24.2% versus 6.5%), dizziness (21.9% versus 6.0%), insomnia (14.5% versus 4.3%) and headache (12.6% versus 9.5%) compared with placebo plus PI, respectively. As noted in the MS (p132-133), the onset of frequent adverse events in the nalmefene plus PI group occurred within a day after the first dose for nausea, dizziness, fatigue, and somnolence and within approximately 1 week for insomnia, headache, and vomiting. The duration was typically a few days (despite a presumed typographical error in the text [p132, MS], the median duration was ≤ 8 days for all the frequent adverse events in the nalmefene group [p132, Table B34, MS]).

In the total population of the ESENSE and SENSE trials, the incidence of treatment emergent adverse events was similar to that observed for the licensed populations (855/1144 [74.7%] versus 500/797 [62.7%], respectively). Further details are provided in Table 13. As noted in the MS (p131-132), the onset and duration of frequent adverse events in the nalmefene plus PI group were similar to those observed for the licensed population.

Table 12: Treatment-emergent adverse events with an incidence of ≥ 5% in either treatment group in patients with a high/very high drinking risk level at baseline and randomisation: Licensed population (Data derived from p131 of the MS and clarification response to question B19)

Adverse event	ESENSE1		ESENSE2		SENSE		Pooled	
	Nalmefene + PI (n=179)	Placebo + PI (n=169)	Nalmefene + PI (n=152)	Placebo + PI (n=158)	Nalmefene + PI (n=144)	Placebo + PI (n=42)	Nalmefene + PI (n=475)	Placebo + PI (n=369)
Patients with treatment-emergent adverse events	149 (83.2%)	124 (73.4%)	107 (70.4%)	96 (60.8%)	112 (77.8%)	26 (61.9%)	368 (77.5%)	246 (66.7%)
Nausea	51 (28.5%)	12 (7.1%)	27 (17.8%)	11 (7.0%)	37 (25.7%)	1 (2.4%)	115 (24.2%)	24 (6.5%)
Dizziness	56 (31.3%)	12 (7.1%)	22 (14.5%)	9 (5.7%)	26 (18.1%)	1 (2.4%)	104 (21.9%)	22 (6.0%)
Insomnia	20 (11.2%)	3 (1.8%)	29 (19.1%)	12 (7.6%)	20 (13.9%)	1 (2.4%)	69 (14.5%)	16 (4.3%)
Headache	27 (15.1%)	18 (10.7%)	19 (12.5%)	15 (9.5%)	14 (9.7%)	2 (4.8%)	60 (12.6%)	35 (9.5%)
Fatigue	30 (16.8%)	16 (9.5%)	NR	NR	9 (6.3%)	2 (4.8%)	43 (9.1%)	22 (6.0%)
Vomiting	15 (8.4%)	5 (3.0%)	10 (6.6%)	7 (4.4%)	15 (10.4%)	1 (2.4%)	40 (8.4%)	13 (3.5%)
Nasopharyngitis	18 (10.1%)	27 (16.0%)	8 (5.3%)	9 (5.7%)	12 (8.3%)	3 (7.1%)	38 (8.0%)	39 (10.6%)
Sleep disorder	28 (15.6%)	1 (0.6%)	NR	NR	NR	NR	32 (6.7%)	4 (1.1%)
Hyperhidrosis	11 (6.1%)	3 (1.8%)	NR	NR	10 (6.9%)	0	28 (5.9%)	3 (0.8%)
Decreased appetite	11 (6.1%)	3 (1.8%)	8 (5.3%)	1 (0.6%)	8 (5.6%)	0	27 (5.7%)	4 (1.1%)
Diarrhoea	8 (4.5%)	12 (7.1%)	4 (2.6%)	9 (5.7%)	NR	NR	19 (4.0%)	22 (6.0%)
Accidental overdose	4 (2.2%)	11 (6.5%)	NR	NR	5 (3.5%)	4 (9.5%)	13 (2.7%)	22 (6.0%)
Back pain	10 (5.6%)	9 (5.3%)	NR	NR	NR	NR	NR	NR
Dry mouth	9 (5.0%)	3 (1.8%)	NR	NR	NR	NR	NR	NR
Hypoaesthesia	9 (5.0%)	1 (0.6%)	NR	NR	NR	NR	NR	NR
Tremor	NR	NR	8 (5.3%)	7 (4.4%)	NR	NR	NR	NR
Somnolence	NR	NR	NR	NR	10 (6.9%)	3 (7.1%)	NR	NR
Tachycardia	NR	NR	NR	NR	10 (6.9%)	0	NR	NR
Fall	NR	NR	NR	NR	3 (2.1%)	4 (9.5%)	NR	NR
Contusion	NR	NR	NR	NR	2 (1.4%)	3 (7.1%)	NR	NR

Lower respiratory tract infection	NR	NR	NR	NR	0	3 (7.1%)	NR	NR
PI, Psychosocial Intervention, NR, not reported								

Table 13: Treatment-emergent adverse events with an incidence of ≥ 5% in either treatment group: Total population (Data derived from p130 of the MS and clarification response to question B19)

Adverse event	ESENSE1		ESENSE2		SENSE		Pooled	
	Nalmefene + PI (n=302)	Placebo + PI (n=296)	Nalmefene + PI (n=341)	Placebo + PI (n=337)	Nalmefene + PI (n=501)	Placebo + PI (n=164)	Nalmefene + PI (n=1144)	Placebo + PI (n=797)
Patients with treatment-emergent adverse events	246 (81.5%)	198 (66.9%)	232 (68.0%)	199 (59.1%)	377 (75.2%)	103 (62.8%)	855 (74.7%)	500 (62.7%)
Nausea	83 (27.5%)	18 (6.1%)	58 (17.0%)	20 (5.9%)	112 (22.4%)	9 (5.5%)	253 (22.1%)	47 (5.9%)
Dizziness	83 (27.5%)	23 (7.8%)	52 (15.2%)	15 (4.5%)	73 (14.6%)	6 (3.7%)	208 (18.2%)	44 (5.5%)
Insomnia	30 (9.9%)	10 (3.4%)	49 (14.4%)	22 (6.5%)	74 (14.8%)	11 (6.7%)	153 (13.4%)	43 (5.4%)
Headache	36 (11.9%)	27 (9.1%)	43 (12.6%)	26 (7.7%)	62 (12.4%)	13 (7.9%)	141 (12.3%)	66 (8.3%)
Nasopharyngitis	34 (11.3%)	37 (12.5%)	19 (5.6%)	17 (5.0%)	54 (10.8%)	19 (11.6%)	107 (9.4%)	73 (9.2%)
Vomiting	24 (7.9%)	8 (2.7%)	19 (5.6%)	8 (2.4%)	57 (11.4%)	2 (1.2%)	100 (8.7%)	18 (2.3%)
Fatigue	53 (17.5%)	25 (8.4%)	NR	NR	27 (5.4%)	3 (1.8%)	95 (8.3%)	37 (4.6%)
Somnolence	NR	NR	NR	NR	42 (8.4%)	8 (4.9%)	59 (5.2%)	23 (2.9%)
Sleep disorder	32 (10.6%)	1 (0.3%)	NR	NR	NR	NR	NR	NR
Hyperhidrosis	16 (5.3%)	5 (1.7%)	NR	NR	NR	NR	NR	NR
Decreased appetite	26 (5.2%)	2 (1.2%)	NR	NR	26 (5.2%) [a]	2 (1.2%) [a]	NR	NR
Diarrhoea	8 (2.3%)	17 (5.0%)	NR	NR	NR	NR	NR	NR
Accidental overdose	9 (1.8%)	9 (5.5%)	NR	NR	9 (1.8%) [a]	9 (5.5%) [a]	NR	NR
Fall	7 (1.4%)	11 (6.7%)	NR	NR	7 (1.4%) [a]	11 (6.7%) [a]	NR	NR

PI, Psychosocial Intervention, NR, not reported
[a] Data from Van den Brink *et al*.[34]

Superseded – see Erratum

The incidence of serious adverse events (no definition was provided in the MS; however, a detailed list of serious adverse events was provided) in the pooled subgroup of people with at least a high drinking risk level at screening and randomisation (licensed population) was higher in the nalmefene plus PI group (26/475 [5.5%]) compared with the placebo plus PI (13/369 [3.5%]) group (p-value not reported). A summary of the serious treatment-related adverse events, as reported by the manufacturer and adapted (data re-tabulated in a consistent and more transparent format) by the ERG is presented in Table 14.

In the pooled total populations of the ESENSE1, ESENSE2 and SENSE trials, the incidence of serious adverse events was similar to that observed in the licensed populations (57/1144 [5.0%] versus 35/797 [4.4%], respectively). Further details are provided in Table 15.

Table 14: Serious adverse events in >1 patient in either treatment group: Licensed population (Data derived from p136 of the MS and clarification response to question B19)

Adverse event	ESENSE1		ESENSE2		SENSE		Pooled	
	Nalmefene + PI (n=179)	Placebo + PI (n=169)	Nalmefene + PI (n=152)	Placebo + PI (n=158)	Nalmefene + PI (n=144)	Placebo + PI (n=42)	Nalmefene + PI (n=475)	Placebo + PI (n=369)
Patients with treatment-emergent serious adverse events	11 (6.1%)	5 (3.0%)	4 (2.6%)	7 (4.4%)	11 (7.6%)	1 (2.4%)	26 (5.5%)	13 (3.5%)
Alcoholism	NR	NR	NR	NR	NR	NR	2 (0.4%)	1 (0.3%)
Fall	NR	NR	NR	NR	NR	NR	2 (0.4%)	1 (0.3%)
Noncardiac chest pain	NR	NR	NR	NR	NR	NR	2 (0.4%)	0
Pneumothorax	NR	NR	NR	NR	NR	NR	0	2 (0.5%)
Rib fracture	NR	NR	NR	NR	NR	NR	0	2 (0.5%)

PI, Psychosocial Intervention, NR, not reported

Table 15: Serious adverse events in >1 patient in either treatment group: Total population (Data derived from p135 of the MS and clarification response to question B19)

Adverse event	ESENSE1		ESENSE2		SENSE		Pooled	
	Nalmefene + PI (n=302)	Placebo + PI (n=296)	Nalmefene + PI (n=341)	Placebo + PI (n=337)	Nalmefene + PI (n=501)	Placebo + PI (n=164)	Nalmefene + PI (n=1144)	Placebo + PI (n=797)
Patients with treatment-emergent serious adverse events	17 (0.7%)	16 (5.4%)	6 (1.8%)	11 (3.3%)	34 (6.8%)	8 (4.9%)	57 (5.0%)	35 (4.4%)
Alcohol withdrawal syndrome	NR	NR	NR	NR	8 (1.6%)	1 (0.6%)	8 (0.7%)	1 (0.1%)
Alcoholism	2 (0.3%)	2 (0.7%)	NR	NR	NR	NR	4 (0.3%)	2 (0.3%)
Fall	NR	NR	NR	NR	2 (0.4%)	0	3 (0.3%)	1 (0.1%)
Alcohol poisoning	NR	NR	NR	NR	NR	NR	2 (0.2%)	2 (0.3%)
Atrial fibrillation	NR	NR	NR	NR	2 (0.4%)	0	2 (0.2%)	0
Depression	NR	NR	NR	NR	NR	NR	2 (0.2%)	0
Disorientation	NR	NR	NR	NR	2 (0.4%)	0	2 (0.2%)	0
Noncardiac chest pain	NR	NR	NR	NR	NR	NR	2 (0.2%)	0
Alcohol abuse	NR	NR	NR	NR	NR	NR	1 (0.1%)	2 (0.3%)
Fibula fracture	NR	NR	NR	NR	NR	NR	1 (0.1%)	2 (0.3%)
Pneumonia	NR	NR	NR	NR	NR	NR	1 (0.1%)	2 (0.3%)
Completed suicide	0	2 (0.7%)	NR	NR	NR	NR	0	2 (0.3%)
Convulsion	0	2 (0.7%)	NR	NR	NR	NR	0	2 (0.3%)
Hypertension	NR	NR	NR	NR	NR	NR	0	2 (0.3%)
Intentional overdose	NR	NR	0	2 (0.6%)	NR	NR	0	2 (0.3%)

Pneumothorax	NR	NR	NR	NR	NR	NR	0 (0.0)	2 (0.3)
Pyothorax	NR	NR	NR	NR	NR	NR	0 (0.0)	2 (0.3)
Rib fracture	NR	NR	NR	NR	NR	NR	0 (0.0)	2 (0.3)
Tibia fracture	NR	NR	NR	NR	NR	NR	0 (0.0)	2 (0.3)

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.3.1 Naltrexone (p61-63 and 107-124, MS)

In the absence of any direct head-to-head RCTs comparing nalmefene plus PI with naltrexone plus PI, the manufacturer investigated whether a network meta-analysis or indirect comparison could be conducted to estimate the effect of naltrexone plus PI with nalmefene plus PI for the reduction of alcohol consumption in actively drinking adults with mild alcohol dependence. The manufacturer's systematic review used the same approach (e.g. literature searching, study selection, data extraction and quality assessment) that was undertaken for the nalmefene systematic review but only included studies that investigated oral naltrexone (50mg) plus any type of PI or best supportive care with placebo plus PI or best supportive care. Drinking outcomes that were considered relevant included the following: level of alcohol consumption; number of drinks per day; and number of heavy drinking days or percentage of heavy drinking days (p61-63, p107-108, p111-119 of the MS and clarification response to questions B1, B16 and B18).

The manufacturer's systematic review identified three RCTs (representing four citations[42-45]) of varying methodological quality, that compared oral naltrexone (50 mg/day) plus PI with placebo plus PI in actively drinking adults with alcohol dependence. A summary of the study design characteristics and results, as reported in the MS, is provided in Table 16 (further data are reported in the MS, p115-118). As noted in the MS (p124) all identified studies had limitations in the reporting of data (not reporting values for total alcohol consumption, not reporting drinking levels at baselines, lack of reported data for the drinking outcomes and not reporting the evaluable number of patients) thus making them ineligible for an indirect comparison of nalmefene plus PI versus placebo plus PI and naltrexone plus PI versus placebo plus PI. The ERG notes that relevant data (e.g. missing information, unpublished data and additional sources of information) may have been obtained by contacting authors of the included naltrexone studies. However, this was not attempted by the manufacturer (manufacturer's clarification response to question B17).

Despite the lack of published data on the use of naltrexone plus PI in actively drinking adults with alcohol dependence, NICE CG115[3] recommends the use of off-label naltrexone for 'people with mild alcohol dependence who have not responded to PI alone, or who have specifically requested a pharmacological intervention'. Currently two versions of naltrexone (50mg) are available: a generic version and a branded version. The generic version (naltrexone) is licensed for use as an additional therapy within a comprehensive treatment programme to support abstinence in alcohol dependence.[46] The branded version (Adepend) is licensed for use as part of a comprehensive programme of treatment against alcoholism to reduce the risk of relapse, as support treatment in abstinence, and to reduce the craving for alcohol.[47] Whilst naltrexone is not explicitly licensed for the reduction of

consumption in people with mild alcohol dependence, the clinical advisors to the ERG state that in accordance with NICE CG115[3] naltrexone is used off-label within specialist services in individuals with mild alcohol dependence who want to reduce their drinking but who have not succeeded with PI alone. The clinical advisors to the ERG also noted that in current practice naltrexone was unlikely to be prescribed by GPs.

Table 16: Summary of identified trials RCTs of oral naltrexone (50 mg) plus PI versus placebo plus PI in alcohol dependence

Study	Design	Population	Treatment groups	Relevant drinking outcomes	Findings and limitations for indirect comparison
Heinälä *et al.*[42]	Randomised double-blind, 32-week placebo-controlled trial conducted in Finland	Outpatients (aged 21 to 65 years) with alcohol dependence (DSM-IV criteria) (n=121)	Naltrexone plus CBT (n=34) Placebo plus CBT (n=33 Naltrexone plus SBT (n=29) Placebo plus SBT: (n=25) (CBT or SBT and either naltrexone 50 mg/day or placebo daily for the first 12 weeks and thereafter naltrexone (undefined dose) given only when alcohol drinking was likely (targeted medication) for 20 weeks)	Total alcohol consumption (g/week) for the last 8 weeks of the 32-week trial for all four groups	Naltrexone plus SBT was worse than placebo plus SBT in reducing alcohol consumption; however, naltrexone plus CBT was better than placebo plus CBT in reducing alcohol consumption. Selective reporting of data in terms of providing final values for total alcohol consumption, with no mention of drinking levels at baseline.
Kranzler *et al.*; Hernandez-Avila *et al.*[43,44]	Randomised, double-blind, 8-week, placebo-controlled pilot study conducted in the USA	Patients (aged 18 to 60 years) with an average weekly alcohol consumption of >24 standard drinks for men and >18 standard drinks for women (78.7% considered alcohol dependent) (n=153)	Daily naltrexone plus CST (n=35) Targeted naltrexone plus CST (n=43) Daily placebo/CST (n=39) Targeted placebo/CST (n=36) (Patients received study medication (i.e. naltrexone 50 mg or placebo) and were instructed to use it either daily or targeted to situations identified by them as being a high risk drinking situation for 8 weeks	Number of drinks/day, percent heavy drinking days	Data reported qualitatively. In general, naltrexone did not significantly reduce alcohol consumption compared with placebo Selective reporting of data for the drinking outcomes. Only baseline data were provided for the number of drinks/day, percent drinking days, and percent heavy drinking days, with no further data provided at the study time points.
Kranzler *et al.*[45]	Randomised, double-blind,	Patients (aged 18 to 65 years) with	Daily naltrexone plus CST (n= 45) Targeted naltrexone plus CST (n=38)	Mean number of drinks per day in	Daily naltrexone was observed not to be better than placebo in terms of reducing

	12-week, placebo-controlled pilot study conducted in the USA	an average weekly alcohol consumption of ≥24 standard drinks for men and ≥18 standard drinks for women (95.1% considered alcohol dependent) (n=163)	Daily placebo plus CST (n=41) Targeted placebo plus CST (n= 39) (Patients received study medication (i.e. naltrexone 50 mg or placebo) and were instructed to use it either daily or targeted to situations identified by them as being high risk for heavy drinking for 12 weeks)	males and females in all four arms at 2, 4, 6, 8, 10 and 12 weeks	the number of drinks per day for both males and females (both subgroups were even drinking more in the daily naltrexone group compared to the placebo group at all follow-ups for females and at all except one for males). The targeted naltrexone group showed not to be better than placebo at the end of the trial (12 weeks) for females. However, a beneficial effect was seen among males. For all patients, difference between the targeted naltrexone group and the mean of other three groups (daily naltrexone, targeted placebo and daily placebo) was not significant (multilevel regression results: b = −0.18, SE = 0.13, *P* = 0.15). Selective reporting of data with no mention of drinking levels at baseline and the evaluable number of patients for the reported subgroups were not reported
CBT, cognitive behavioural therapy; SBT, supportive therapy; CST, coping skills training; SE, standard error					

4.3.2 *Psychological/psychosocial intervention (p108-127, MS)*

The manufacturer conducted a systematic review to identify clinical trials investigating the use of PI in alcohol dependence that were most similar to BRENDA (the PI used in the nalmefene studies). The review updated an existing review of psychosocial comparators that was undertaken to inform NICE CG115,[3] within the context of the manufacturer's systematic review.

The manufacturer's systematic review used a similar approach to that of the nalmefene and naltrexone reviews they had conducted. As the current review was an update of an existing review, all searches were limited by date from September 2009 (last search date, including six month overlap, from earlier review) to December 2013 and English language (further details on search limitations are provided in Section 4.1.1). However, details on how the update was conducted were lacking (e.g. details of data extraction and quality assessment of included studies from the existing review) in the MS. Eligible studies included adults with alcohol dependence. The PI interventions (as specified in the final scope issued by NICE including interventions listed in NICE CG115[3] that were most similar to BRENDA [the psychosocial treatment used in the three nalmefene trials]) included: extended brief interventions and motivational techniques; however the manufacturers also looked at: cognitive behavioural therapies; behavioural therapies; motivational enhancement therapy; and social network and environment therapies. Drinking outcomes that were considered relevant included the following: level of alcohol consumption; number of drinks per day; and number of heavy drinking days or percentage of heavy drinking days.

Superseded – see Erratum

Initially, the manufacturer's systematic review identified 50 potential RCTs. Of these, 43 were identified from the original NICE review and 7 were identified by the updated searches (further details are provided in Table B28, p121-123 of the MS). On further assessment, only 22 studies met the manufacturers systematic review inclusion criteria (motivational techniques, n=5; cognitive behavioural therapies, n=12; behavioural therapies, n=4; and social network and environment based therapies, n=1). Although poorly reported, the ERG assumes that all the excluded studies failed to provide details on relevant outcome data e.g. total daily alcohol consumption and change in number of heavy drinking days. In addition, as noted in the manufacturer's clarification response to question B17, no attempt was made by the manufacturer to contact authors of these excluded PI studies to request potential additional unpublished data.

Although a meta-analysis of the included studies was not undertaken by the manufacturer (no explicit reasons were provided in the MS) a summary of the absolute reductions in drinking that were reported

in the PI trials (including ESENSE1, ESENSE2 and SENSE) as reported by the manufacturer are reproduced, with the correction of typographical errors, in Table 17. As noted in the MS (p108, 125), motivational techniques are the PI most aligned with BRENDA, which was used in the pivotal trials for nalmefene. As shown in Table 17 the absolute reduction in total alcohol consumption from these studies range from 9.3 g per day to 50.7 g per day, with a median value of 18.3 g per day (range of follow-up time: 6 months to 12 months). For the absolute reduction of monthly heavy drinking days, the range was from 1.3 to 19, with a median value of 5.7 (range of follow-up time: 3 months to 12 months). In the pivotal nalmefene trials, the absolute reduction in total alcohol consumption in the nalmefene plus PI group ranged from 58.3 g per day to 70.4 g per day, whereas in the placebo plus PI group the absolute reduction in total alcohol consumption ranged from 40 g per day to 60.1 g per day. The absolute reduction of monthly heavy drinking days in the nalmefene plus PI group ranged from 11.6 to 12.9 whereas in the placebo plus PI group the absolute reduction of monthly heavy drinking days ranged from 8 to 10.2 (range of follow-up time: 6 months to 12 months). The MS (p125) suggest that these findings suggest that the placebo effect has reduced the relative effect of nalmefene plus PI versus PI alone in the RCT context, and that this differential effect is most likely to be higher in real-life practice. Whilst the PI response in the nalmefene pivotal trials is at the upper end of the motivational techniques range, the ERG does not agree that this necessarily results in an unfavourable comparison for nalmefene given the results reported by Hester *et al*.[48] Moreover, as shown in Table 17 the reduction seen in the PI arms of the nalmefene pivotal trials are not high when other forms of PI (Cognitive Behavioural Therapy, Behavioural Therapies and Social Network and Environment Based Therapies) are considered. The compatibility of the PI used in the trials in Table 17 with the PI recommended by NICE CG115 was not assessed by the manufacturer. A brief review was undertaken by the ERG to assess the comparability with the following RCTs being those with at least 9 sessions of at least 45 minutes' duration (or anticipated to last this long where the data were not provided) in an individual setting and without the use of concomitant naltrexone: Alden (Canada – behavioural self-management training arm and developmental counselling arm)[49]; Litt (USA – both arms)[50]; Morgenstern (USA – motivational intervention and cognitive behavioural therapy arm)[51]; Sandahl (Sweden – both arms)[52]; Vedel (Holland – both arms)[53]; and Walitzer (USA – all arms).[54] Further details of these trials can be found in Tables 10-25 to Table 10-29 (pages 327-366) of the MS. Whilst the results of BRENDA plus placebo appear reasonably aligned with the results in these studies, considerable caution should be taken in making comparisons due to potential differences in population characteristics and country; it is commented that only a small minority of patients in ESENSE1, ESENSE2 and SENSE are Swedish, with no patients from the USA, Holland or Canada. In addition considerable caution should be exercised in comparing sessions by length and duration without taking the content of the sessions into account.

Table 17: Summary of results on absolute reduction in drinking reported in the PI trials (reproduced from MS, p126-127)

Reference First Author (PI)	Change from baseline in TAC, g/day [mean]	Change from baseline in HDDs/month
Motivational Techniques		
Davidson 2007 (BST)[55]	N/A	12.7
Davidson 2007 (MET)[55]	N/A	13
Hester 2005 (DCU)[48]	50.7	N/A
Hester 2005 (Control)[48]	43.96	N/A
Rosenblum 2005b (RPME [MET] [Baseline 1-15 HDD])[56]	N/A	5.9
Rosenblum 2005b (Control [Baseline 1-15 HDD])[56]	N/A	1.3
Rosenblum 2005b (RPME [MET] [Baseline 16-30 HDD])[56]	N/A	19
Rosenblum 2005b (Control [Baseline 16-30 HDD])[56]	N/A	4.11
Shakeshaft 2002 (FRAMES)[57]	11.1	7.8
Shakeshaft 2002 (CBT)[57]	9.3	5.5
Sobell 2002 (MET)[58]	19.4	4.75
Sobell 2002 (PSYEDU)[58]	17.2	4.13
Cognitive Behavioural Therapies		
Davidson 2007 (BST)[55]	N/A	12.7
Davidson 2007 (MET)[55]	N/A	13
Litt 2009 (PCBT)[50]	N/A	11.2
Litt 2009 (IATP)[50]	N/A	12.9
Marques 2001 (GR CBT)[59]	34.3	6.7
Marques 2001 (IND CBT)[59]	25.7	6
Monti 1990 (CST)[60]	141.68	10.12
Monti 1990 (CSTF)[60]	159.04	11.36
Monti 1990 (CBMMT)[60]	71.96	5.14
Monti 1993 (CE+CS [CBT])[61]	182	13
Monti 1993 (TAU)[61]	84	6
Morgenstern 2007 (MI + CBT)[51]	56.84	N/A
Morgenstern 2007 (MI)[51]	48.58	N/A
Rosenblum 2005b (RPME [Baseline 1-15 HDD])[56]	N/A	5.9
Rosenblum 2005b (Control [Baseline 1-15 HDD])[56]	N/A	1.3
Rosenblum 2005b (RPME [Baseline 16-30 HDD])[56]	N/A	19
Rosenblum 2005b (Control [Baseline 16-30 HDD])[56]	N/A	4.11
Sandahl 1998 (RP)[52]	N/A	6.7
Sandahl 1998 (PSYDY)[52]	N/A	6.7
Shakeshaft 2002 (FRAMES)[57]	11.1	7.8
Shakeshaft 2002 (CBT)[57]	9.3	5.5
Sobell 2009 (Group GSC)[62]	N/A	6.57

Sobell 2009 (Individual GSC)[62]	N/A	7.38
Vedel 2008 (CBT)[53]	52.13	N/A
Vedel 2008 (BCT)[53]	50.21	N/A
Walitzer 2009 (CS)[54]	N/A	5.88
Walitzer 2009 (DIR+CS)[54]	N/A	7.28
Walitzer 2009 (MOT+CS)[54]	N/A	5.88
Behavioural Therapies		
Alden 1988 (BSMT)[49]	41.75	N/A
Alden 1988 (Counselling)[49]	48.79	N/A
Kavanagh 2006 (CBT [men])[63]	22.9	N/A
Kavanagh 2006 (CBT [women])[63]	10	N/A
Kavanagh 2006 (CE [men])[63]	18.6	N/A
Kavanagh 2006 (CE [women])[63]	2.9	N/A
Kavanagh 2006 (ECE [men])[63]	5.7	N/A
Kavanagh 2006 (ECE [women])[63]	8.6	N/A
Monti 1993 (CE+CS [CBT])[61]	182	13
Monti 1993 (TAU)[61]	84	6
Walitzer 2004 (BSM)[64]	N/A	0.9
Walitzer 2004 (AFSI)[64]	N/A	1.7
Walitzer 2004 (BCT)[64]	N/A	2.3
Social Network and Environment Based Therapies		
Leigh 1999 (OB)[65]	122.4	N/A
Leigh 1999 (VS)[65]	129.2	N/A
Pivotal Nalmefene Studies		
ESENSE 1 (Nalmefene + BRENDA)[28]	58.3	11.6
ESENSE 1 (Placebo + BRENDA)[28]	40	8
ESENSE 2 (Nalmefene + BRENDA)[31]	70.4	12.9
ESENSE 2 (Placebo + BRENDA)[31]	60.1	10.2
SENSE (Nalmefene + BRENDA)[32]	67.1	12.2
SENSE (Placebo+ BRENDA)[32]	49.8	8.6

AFSI = Alcohol Focused Spousal Involvement; ATP = Assessment Treatment Program; BCT= behavioural couples therapy; BSM= behavioural self-management; BSMT= behavioural self-management training; BST = broad spectrum therapy; CBMMT = Cognitive Behavioural Mood Management Training; CBT= cognitive behavioural therapy; CE = cue exposure; CM=contingency management; CS = coping skills; CST = communication skills training; CSTF = CST with family training; DCU = drinkers check-up; DIR = twelve-step facilitation directive approach; ECE = emotional cue exposure; FRAMES= feedback, responsibility, advice, menu, empathy, self-efficacy; GSC=guided self-change; GR = group therapy; HDD= heavy drinking days; IATP = individual assessment treatment programme; IND = individual therapy; MET= motivational enhancement therapy; MI = motivational intervention; MOT = motivational therapy; NA = not applicable; OB = office based; PCBT = packaged CBT programme; PSYEDU = Bibliotherapy/ Drinking Guidelines; RPME = Relapse Prevention + information and referral; TAC= total alcohol consumption; TAU= treatment as usual; TSF= twelve step facilitation; VS = volunteer support

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparison was undertaken by the manufacturer who stated (p21, MS) that it was not possible to perform an indirect comparison of naltrexone plus PI versus nalmefene plus PI which fulfilled the requirements of good practice for evidence synthesis required by NICE. The ERG agreed with this position.

4.5 Additional clinical exploratory analyses undertaken by the ERG

As the manufacturer undertook a comprehensive systematic review (no major limitations were noted) of nalmefene for the reduction of alcohol consumption in people with alcohol dependence, no additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the MS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence in the MS is based on a systematic review of nalmefene plus PI for the reduction of alcohol consumption in people with presumed mild alcohol dependence. The ERG is confident that all relevant studies (published and unpublished) of nalmefene plus PI were included in the MS, including data from ongoing/planned studies. Although the ERG is confident that no published comparator studies of naltrexone are likely to have been missed, it is not entirely clear if all relevant data have been included as no attempt was made by the manufacturer to contact authors of the included naltrexone studies to request potential additional unpublished data.

4.6.2 Interpretation of treatment effects reported in the MS in relation to relevant population, interventions, comparator and outcomes

A key issue that may limit the robustness of the efficacy and safety data reported in the MS relates to the post-hoc subgroup analyses of participants from the ESENSE and SENSE trials that had a high or very high drinking risk level at screening and randomisation (the subsequent licensed population). As the studies were not powered for these post-hoc subgroup analyses, the effect of initial randomisation may have been lost. In addition to the known limitations of post-hoc subgroup analyses[66], Sun *et al*.[67] also suggest that the credibility of subgroup effects, even when claims are strong, is usually low. However, a scientific advisory group, which was consulted by the EMA during the regulatory process for nalmefene, recognised the validity of the post-hoc analysis defining the target population and acknowledged that whilst post-hoc analyses are not ideal, they are commonly used in clinical trials for psychiatric drugs.[15]

Another issue that may limit the robustness of the evidence relates to the high dropout rates in the three nalmefene studies. In the original ESENSE1 (nalmefene 53.0% versus placebo 30.7%),

ESENSE2 (41.1% versus 37.7%) and SENSE (38.1% versus 31.7%) studies the dropout rates were higher with nalmefene plus PI than placebo PI, respectively (similar rates of discontinuation were observed in the licensed population, Table 10). In general, the validity of a study may be threatened if attrition is more than 20%.[39] Despite the high withdrawal rates in the three nalmefene trials, the EMA assessment report[15] stated that the proportion of patients who withdrew from the nalmefene studies was comparable to that in other placebo-controlled studies conducted in patients with alcohol dependence over the last ten years. In addition, various sensitivity analyses were undertaken by the manufacturer to account for missing data using different imputation methodologies. Although all the sensitivity analyses were in favour of nalmefene, irrespective of imputation method, some inconsistencies were observed in whether statistical significance was achieved or not, thus the EMA noted a degree of uncertainty about the exact magnitude of benefit. To avoid the issue of which was the most appropriate analysis, a further analysis was conducted in 'completers', in which all withdrawals were treated as non-responders. These analyses confirmed the results of the primary analysis (see section 4.2.4.1) that was undertaken using the mixed model repeated measures approach.

Finally, in the nalmefene trials all participants self-reported their alcohol intake, thus this subjective measure could have biased the results. However, the MS (p78) notes that the timeline follow-back method, as used in the ESENSE and SENSE trials, is widely used in alcohol dependence trials and gives reliable retrospective self-reports of drinking in outpatients.[35-38]

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The key uncertainties in the clinical evidence primarily relate to different types or frequencies of PI, duration of treatment and generalisability to the UK population. Further details are provided below.

Different types or frequencies of PI

In the ESENSE1, ESENSE2 and SENSE trials, PI in the form of BRENDA was employed. This was used in accordance with the EMA guideline on the development of medicinal products for the treatment of alcohol dependence,[17] which states that standardised psychosocial interventions should be allowed in alcohol dependence studies and kept to a constant and low level for all patients (p26, MS). In the nalmefene trials, BRENDA was delivered at weekly intervals for the first 2 weeks and monthly thereafter (sessions were limited to approximately 15 to 30 minutes except for the first session which was administered at randomisation and lasted approximately 30 to 40 minutes). This is in stark contrast to the recommendations within NICE CG115,[3] which recommends that PI (including behavioural therapies, cognitive behavioural therapy and behavioural couples therapies) should consist typically of weekly sessions of 1 hour's duration over a 12-week period and be delivered typically by a clinical psychologist. (Sections 6.24.1.15 – 6.24.1.18 and Table 85 of NICE CG115).[3]

It is not clear how the results would apply to people who receive different forms or frequencies of PI. In addition, access to PI that is focused on alcohol use is limited in England.[68]

Duration of treatment

The duration of treatment in the nalmefene trials ranged from 6 months (ESENSE 1 and ESENSE2) to one year (SENSE trial). As a result, efficacy and safety of nalmefene after 12 months is unknown. The Summary of Product Characteristics (SPC) for nalmefene also advises caution if prescribed for more than one year.[14] In addition, the adherence ranged from 75.7% in ESENSE 1 to 86.7% in the SENSE trial in the licensed population.

Generalisability to the population of England and Wales

The total populations in the ESENSE1, ESENSE2 and SENSE trials were predominantly white (>99%) with a mean age of 48 years in the ESENSE trials and 44 years in the SENSE trial. The ESENSE1 and ESENSE2 trials excluded patients with co-morbid psychiatric conditions and SENSE excluded patients with severe psychiatric conditions. However, the MS (p142) suggest that many alcohol-dependent patients have diagnosed medical conditions and/or psychiatric comorbidities. Therefore, it is unclear how well the study results can be extrapolated to older people, non- Caucasian populations or people with mental health conditions. In addition, patients were also excluded from the nalmefene trials if they were taking certain concomitant medication such as drugs for angina, anticoagulants, anticonvulsants, insulin, sedatives, and systemic steroids. As a result, the efficacy and safety profile of nalmefene in people who use these medications is uncertain. Furthermore, only a small minority of people within the pivotal studies were from the UK and no data were provided in the MS on the variability of the outcomes between recruiting European countries. As such there is some uncertainty regarding the generalisability of these data to people in England and Wales.

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 State objective of cost effectiveness review. Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate. If the manufacturer did not perform a systematic review, was this appropriate?

The manufacturer performed a search of the published medical literature to identify published cost-effectiveness analyses for nalmefene in people with alcohol dependence. The search was performed in January 2013 (no reason was provided in the MS for this early search date) in the following databases: MEDLINE; MEDLINE in Process; EMBASE; and the Cochrane Collaboration. In the cost-effectiveness searches, the reported population terms in the database strategies were considered comprehensive by the ERG. However, the free-text terms for nalmefene i.e 'revex' or 'selincro' were omitted from the strategies. Given the low number of records for the intervention alone, the ERG recommends that the intervention should be combined with the cost-effectiveness filter alone. Since the economic evaluation searches were carried out in January 2013, the ERG updated the searches on 27th March 2014 to find studies on nalmefene that might have been published since then. With the suggested approach, the ERG retrieved a total of 35 records in MEDLINE, EMBASE, EconLit and NHS EED.

Although the manufacturer did not undertake any searches to identify published cost effectiveness analyses of naltrexone in people with alcohol dependence, the ERG's cost-effectiveness searches identified a total of 406 unique records on the 27th March 2014. The cost-effectiveness search strategies for naltrexone are included in Appendix 3 of the ERG report.

5.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The search strategy used by the manufacturer is contained in Appendix 10.12 of the MS (p370-371). This was a broad search although it was limited to nalmefene only.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the most important cost effectiveness studies.

The manufacturer identified no published cost effectiveness analysis of nalmefene. In the updated search the ERG also reached this conclusion. In the search for naltrexone studies one study was identified that could have possibly informed the *de novo* economic model. This was authored by Walters *et al.*[69] and assessed the cost-effectiveness of adding naltrexone to cognitive-behavioural therapy in those with alcohol dependence.

The manufacturer did not conduct a search for the cost-effectiveness of PI alone, although this formed a reasonably large part of NICE CG115. NICE CG115 stated that 'Overall, the health economic review does not provide evidence of superior cost effectiveness for any particular PI.'

Given the licensed population of nalmefene it is unlikely that any of the studies identified in NICE CG115 or that of Walters *et al.*[69] would be appropriate, and / or fit the NICE reference case. As such, the ERG is satisfied with the decision by the manufacturer to build a *de novo* model.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

As no studies were identified by the manufacturer the conclusion drawn was that a *de novo* model was required.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 Objective of the model, intervention and comparator

The objective of the model was to estimate the costs incurred and quality adjusted life years (QALYs) accrued by two competing strategies: providing PI alone (the comparator); or providing nalmefene (18mg), dosing as required, in addition to PI (the intervention). It was assumed that both strategies would be provided for at least a period of 12 months unless patients discontinued treatment. The base case analyses presented were in line with NICE's reference case.

Within the model the PI component was assumed to be represented by BRENDA as employed in the ESENSE1[28], ESENSE2[31] and SENSE[32] RCTs, as detailed in Section 4.2.1. BRENDA was provided at weeks 0, 1, 2, 4, 8, 12, 16, 20 and 24 and thus there were 6 sessions with trained personnel within the first twelve weeks, with each session being between 15 and 30 minutes, except for the first session which lasted approximately 30 to 40 minutes. As such, BRENDA as used in the pivotal RCTs contrasts strongly with NICE CG115[3] which states that therapies should usually consist of one 60-minute session per week for 12 weeks. Therefore, the evaluation undertaken in the model does not meet that specified in the final scope[70] which stipulates that the comparator should be PI (as defined in NICE CG115)

The manufacturer assumed that BRENDA would be performed by GPs on 75% of occasions with the remaining 25% performed at a specialist level. The clinical advisors to the ERG disagreed with this assumption stating that the proportion undertaken in specialist care would be much higher were best practice followed; NICE CG115 states that 'all interventions for people who misuse alcohol should be delivered by appropriately trained and competent staff.'

Naltrexone was not formally modelled as a comparator by the manufacturer despite being within the final scope.[70]

5.2.2 The population modelled

The population modelled was that as stated in the final scope[70] which was 'Adults with mild alcohol dependence (as defined in NICE CG115[3]) who have a high-risk drinking level (≥ 60 g/day of pure alcohol for men and ≥ 40 g/day for women) without physical withdrawal symptoms and who do not require immediate detoxification'. However, the population was appropriately restricted to those that had received a brief intervention yet remained at a high- or very high-risk drinking level two weeks following the intervention.

The model uses pooled data from the licensed population subgroups of three RCTs: ESENSE1[28], ESENSE2[31] and SENSE.[32] In accordance with data from these RCTs the mean age of the hypothetical patients at the start of the model was assumed to be 48 years with 69% assumed to be male.

5.2.3 The model structure

The manufacturer submitted a state transition cohort model written in Microsoft Excel (©Microsoft Corporation, Redmond, Washington). The model used a time horizon of 5 years, with the initial year using a cycle length of one month whilst years 2 to 5 employed cycle lengths of one year. The ERG and the clinical advisors to the ERG consider that the time horizon is appropriate given the potential for drinking status to be affected by life experiences; although it may be unfavourable to nalmefene if it is associated with lower mortality rates. Costs incurred and QALYs accrued are both discounted at a rate of 3.5% per annum in line with recommendations from NICE.[18] Half cycle correction was not performed. The two reasons stated by the manufacturer for this, in response to clarification question C3 were that:

1. 'Our model has a short cycle length (1 month) for the first year, and the comparative effect between cohorts seen during the first year is driving the cost-effectiveness conclusion of the analysis. As reported by Sonnenberg & Beck [71], a 1-month cycle length is minimal compared to the relative to average survival, and this lead to believe to a negligible effect of half cycle correction in our case'. [Note: grammatical errors by the manufacturer not corrected in case the ERG misinterpreted the point being made]

2. 'As shown by Naimark *et al.*,[72] half cycle correction is believed to lead to a too large correction when a much larger proportion of subjects still inhabit non-absorbing states during the model time horizon, which is the case in the current model with a minimal proportion of patients captured by an absorbing state over the model 5-year time horizon.'

The ERG acknowledges that the impact of half cycle correction in the monthly time cycles is likely to be small. However, the ERG believes that omitting half cycle correction in the yearly cycles is a limitation. A more accurate estimation will be obtained by assuming that all events took place midway through the year rather than all occurring at the start of the year.

5.2.4 The health states within the model

The model consisted of a number of drinking level states based on the categories defined by the World Health Organisation in 2000,[73] as provided in Table 1.

In accordance with pooled data from the ESENSE1, ESENSE2 and SENSE RCTs the manufacturer assumed that of those patients who met the nalmefene licensing criteria 57.5% of patients would be in the very high-risk drinking level and 42.5% in the high-risk drinking level on entry to the model.

In addition to drinking level states the model contained health states for patients who: experience serious alcohol attributable harmful events; temporary alcohol attributable harmful events; and for those who die. The manufacturer states that the 'alcohol-attributable harmful events included in the model were chosen because they incur a significant cost for the healthcare system and because the association between alcohol consumption and these events has the strongest published evidence. These events also occur in the assessed population of patients and within the chosen 5-year time horizon. These specific events were also identified and implemented in the model based on the advice received by Lundbeck from clinical and epidemiological experts, including assessment of the available evidence in the literature.' For brevity serious alcohol attributable harmful events will henceforth be termed serious events and temporary alcohol attributable harmful events will be termed temporary events.

Serious events comprised: ischaemic heart disease; haemorrhagic stroke; ischaemic stroke; cirrhosis of the liver; and pancreatitis. Patients experiencing a serious event discontinue treatment immediately and remain in that serious event health state for the remainder of the model or until death. Hence patients can only experience a single serious event. Patients with serious events are not allocated to any drinking risk level on the assumption that the costs incurred and utility loss due to the serious event will be of greater magnitude compared with those associated with drinking risk level. Given the relatively short time horizon this assumption appears reasonable although may be slightly unfavourable to nalmefene. As detailed in the Section 5.2.5.2 and 5.2.6.2, the risks of experiencing a first serious event increases with drinking risk severity.

Temporary events comprised: lower respiratory tract infections; transport-related injuries; and injuries not related to transport. Contrary to the assumptions made following a serious event the drinking risk level of the patient was maintained alongside the temporary health states. Patients experiencing temporary events incur an additional cost and a HRQoL decrement but do not discontinue treatment. Temporary events are modelled as tunnel states and patients may experience more than one temporary event within the model time horizon although not simultaneously. As detailed later, the risks of experiencing a temporary event increases as does the drinking risk severity.

Patients may die at any point in the model. The mortality rate was assumed to be comprised of three distinct elements: mortality associated with experiencing a serious event; mortality associated with experiencing a temporary event; and background mortality associated with other causes, the rates of which were set to that for the age- and gender-matched general population. Experiencing a non-fatal serious or non-fatal temporary event in previous time cycles did not influence the underlying mortality rate. These assumptions are likely to be unfavourable to nalmefene although this impact is reduced to the short time horizon of the model.

Superseded – see Erratum

The model allows patients to discontinue treatment as observed in the RCTs. Patients who discontinued treatment due to nalmefene-related adverse events such as: nausea; dizziness; insomnia; or headaches were assumed to switch to PI alone. The assumption that patients who experience a nalmefene-related adverse event continue with PI rather than discontinue treatment may be favourable to nalmefene. The manufacturer did not consider that such patients could receive off-label naltrexone as a replacement intervention; it is unclear if this were modelled whether this would be favourable or unfavourable to nalmefene. No costs or HRQoL reduction is explicitly associated with adverse events with the manufacturer assuming that costs are negligible and disutility is captured by the EQ-5D estimates in the modified ITT population. However, since both the nalmefene plus PI and PI alone treatments use the same utility values per drinking state it is incorrect that the nalmefene specific adverse events would be appropriately captured, which will be favourable to nalmefene.

Patients who discontinue treatment for non-nalmefene related reasons were assumed to receive no further treatment and to immediately transition to either the very high-risk drinking level state (57.5%) or the high-risk drinking level state (42.5%) with these proportions being those assumed at model entry for the population. Patients receiving no treatment are assumed to remain in their allocated drinking risk level, for the remainder of the initial year.

At the end of the initial 12 months patients are divided into three drinking risk groups: abstinent or low-risk; medium-risk; or high- or very high- risk.

Those patients who are in the high- or very high- risk drinking levels at the end of the initial year were assumed to need medically assisted withdrawal followed by treatment with naltrexone with PI or acamprosate with PI. The support for this assumption was stated to be from clinical experts practising in and/or based in the NHS in England. Patients who have dropped out of nalmefene and PI, or PI treatment alone are assumed to receive medically assisted withdrawal despite the lack of compliance earlier in the model.

Those patients who are in the abstinent or low risk drinking levels at the end of the initial year were assumed to need no further treatment. However, these patients are at risk of relapse. Patients who experience a relapse are allocated to either the very high risk drinking level state (57.5%) or the high risk drinking level state (42.5%). Patients who relapse are assumed to return to the treatment that they were receiving (nalmefene and PI or PI alone) at the end of the initial year (cycle 12). Within years 2 to 5 the costs incurred and QALYs accrued in each cycle for patients who relapse were assumed to equal the average costs, and the average QALYs for patients on nalmefene and PI, or PI alone, within the initial 12 month treatment period.

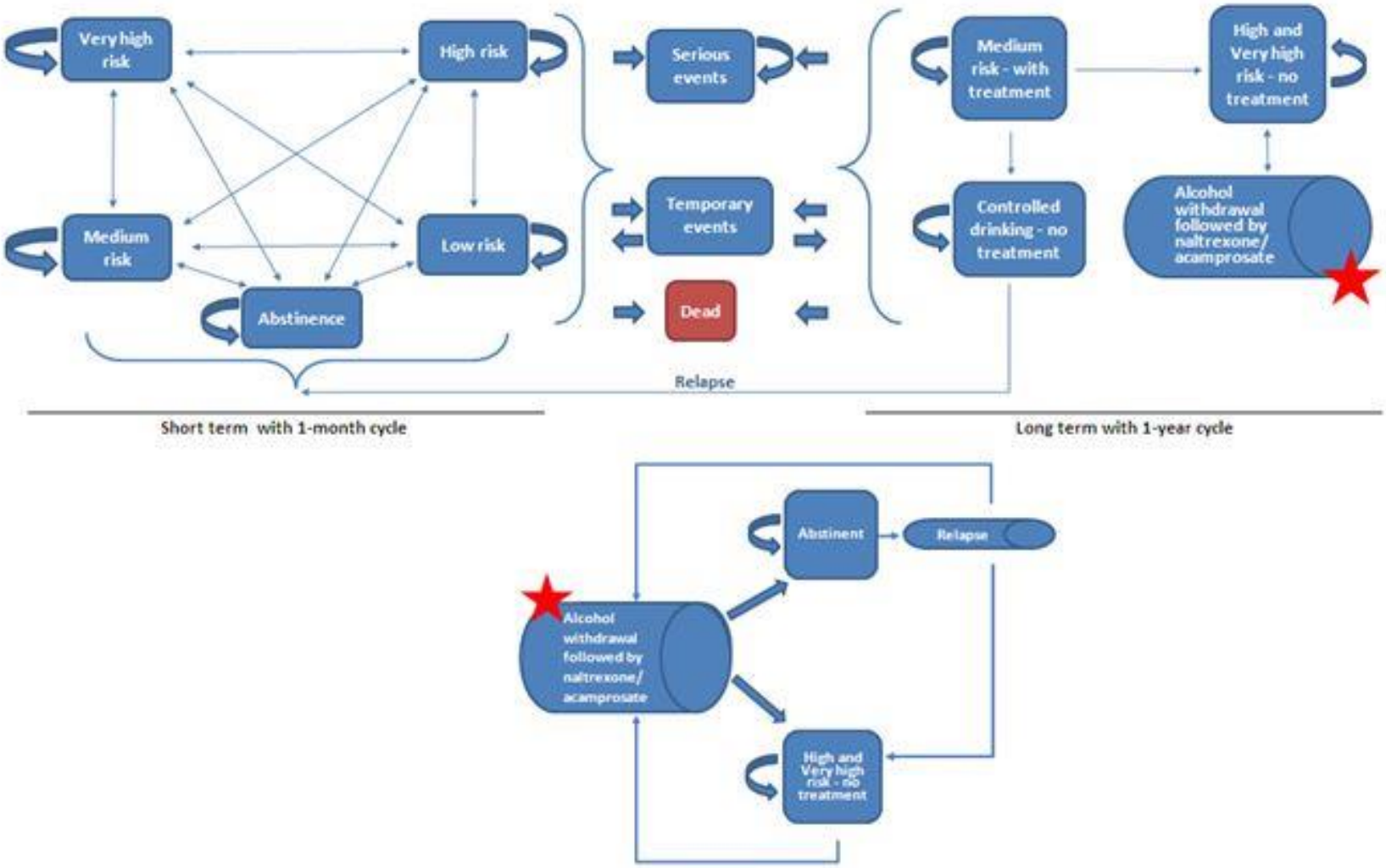
Those patients still drinking at a medium-risk level at 12 months were assumed to carry on with the current treatment, as it was deemed to have produced a response to treatment, but not sufficiently so that treatment should be stopped. It is reported in the MS that 'According to clinical experts in England and Wales consulted by Lundbeck, this is aligned with clinical practice considering the risk of acute and chronic harms for this level of drinking'. Should the patient progress to the abstinent / low-risk drinking levels then treatment would be discontinued; should patients regress to a high- or very high-risk drinking levels then secondary treatment with naltrexone with PI or acamprosate with PI was assumed. The ERG comments that the nalmefene SPC includes that the EMA state that 'Caution is advised if nalmefene is prescribed for more than 1 year.'[14] Following the round of clarification questions the manufacturer amended the model to allow two alternative assumptions to be made (for each strategy) regarding the care pathway of those patients drinking at medium risk following twelve months of treatment. These were assuming all patients received no further treatment and are modelled as though they were abstinent or low-risk drinkers and assuming all patients relapsed to a high- / very high-risk level and received medically assisted withdrawal.

The schematic of the model contained on p159 of the MS has been reproduced in Figure 7.

In addition to the health states reported above, the model can consider a wider societal perspective which incorporates the effect of alcohol consumption on crime and justice. The MS cite Anderson and Baumberg[74] who report that in England and Wales: 25% of all crimes; 48% of violent crime; 19% of robbery; and 58% of sex offenses / rape were undertaken by people under the influence of alcohol, or

were alcohol-related. The manufacturer has applied methods reported by the University of Sheffield[75], which provided evidence for a NICE guideline.[12] The inclusion of a societal perspective is within scenario analyses and is not included within the manufacturer's base case.

Figure 7: The model structure contained within the MS

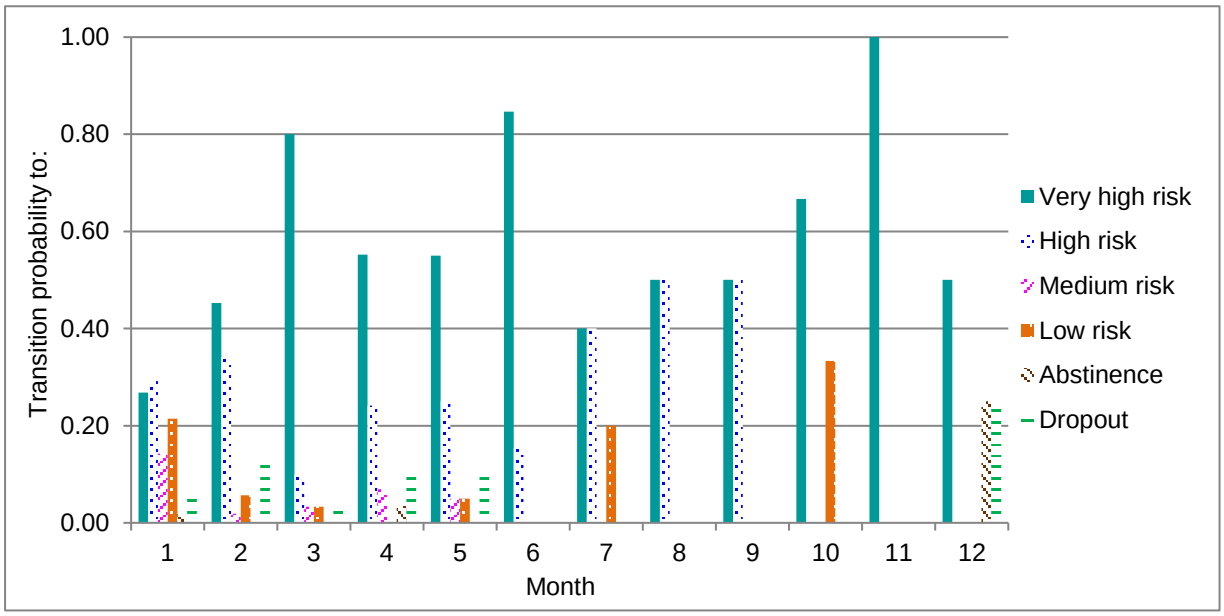


5.2.5 Transition probabilities in the first year

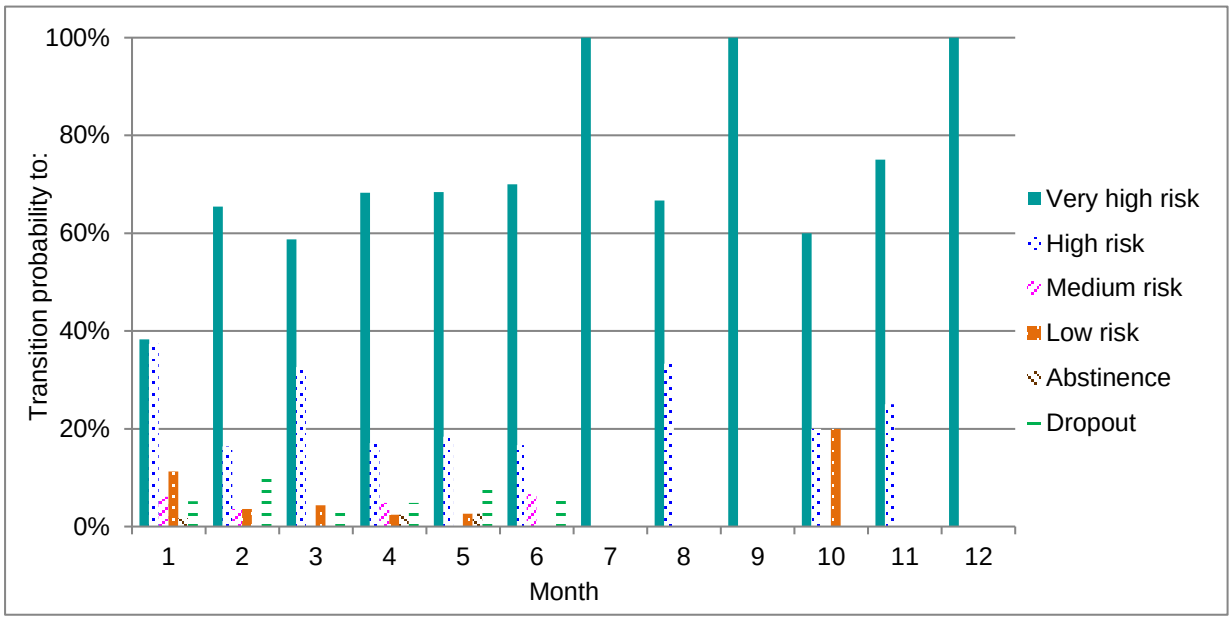
5.2.5.1 Transitions among drinking risk levels in the first year

Transition probabilities for patients changing drinking state in the first year were derived using pooled data from ESENSE1[28], ESENSE2[31] and SENSE trials.[32] The transition probabilities for men changing drinking state for nalmefene plus PI and PI alone over the 12 monthly cycles in the first year are shown in Figures 8, 9, 10, 11 and 12. These have been constructed by the ERG to allow visualisation of these data. The full data (including the transition probabilities for females), are contained in tabular form in the MS on pages 374 to 388.

Figure 8: Transition probabilities assumed in the model in the first year from very high-risk drinking levels

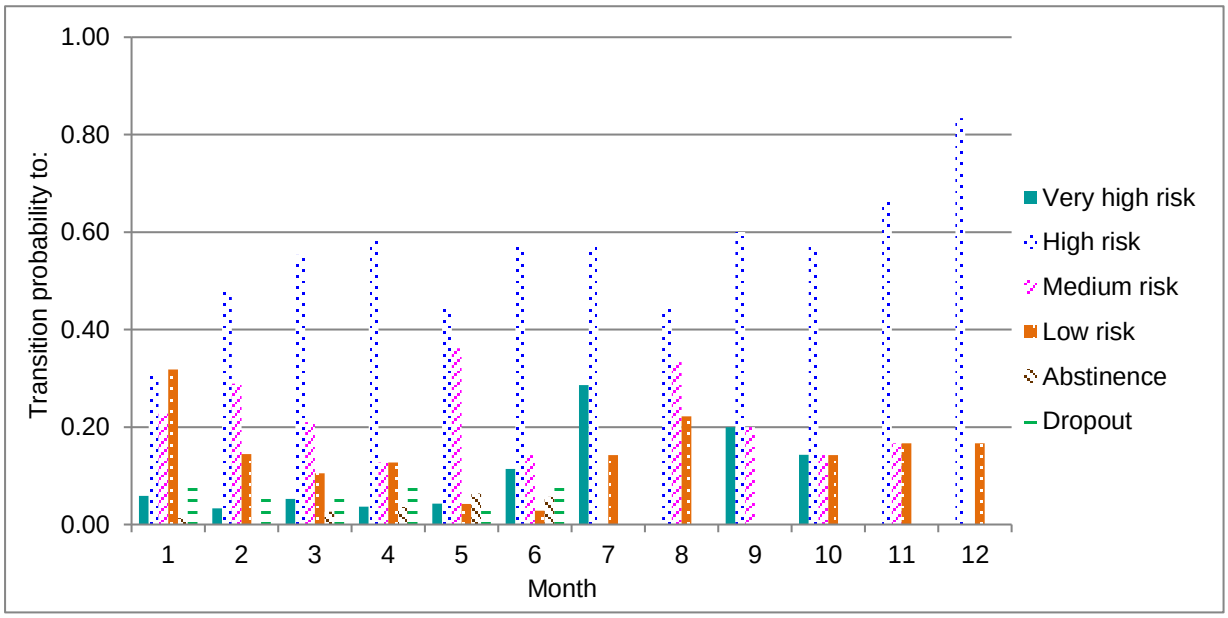


a) PI and nalmefene treated patients

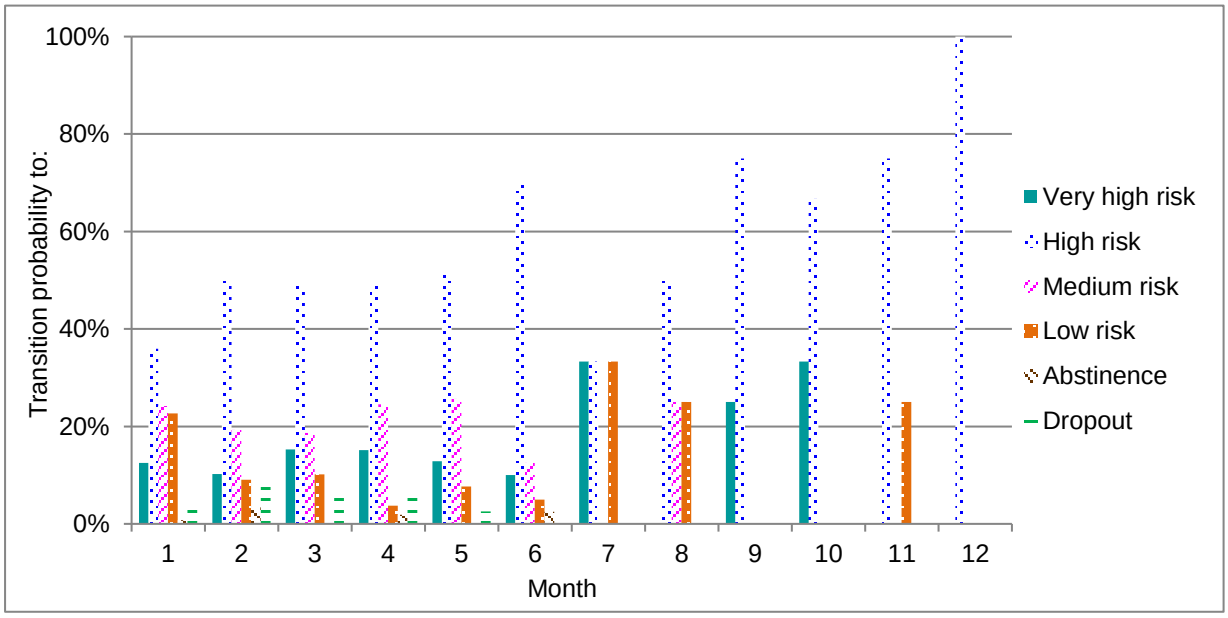


b) PI treated patients

Figure 9: Transition probabilities assumed in the model in the first year from high risk-drinking levels

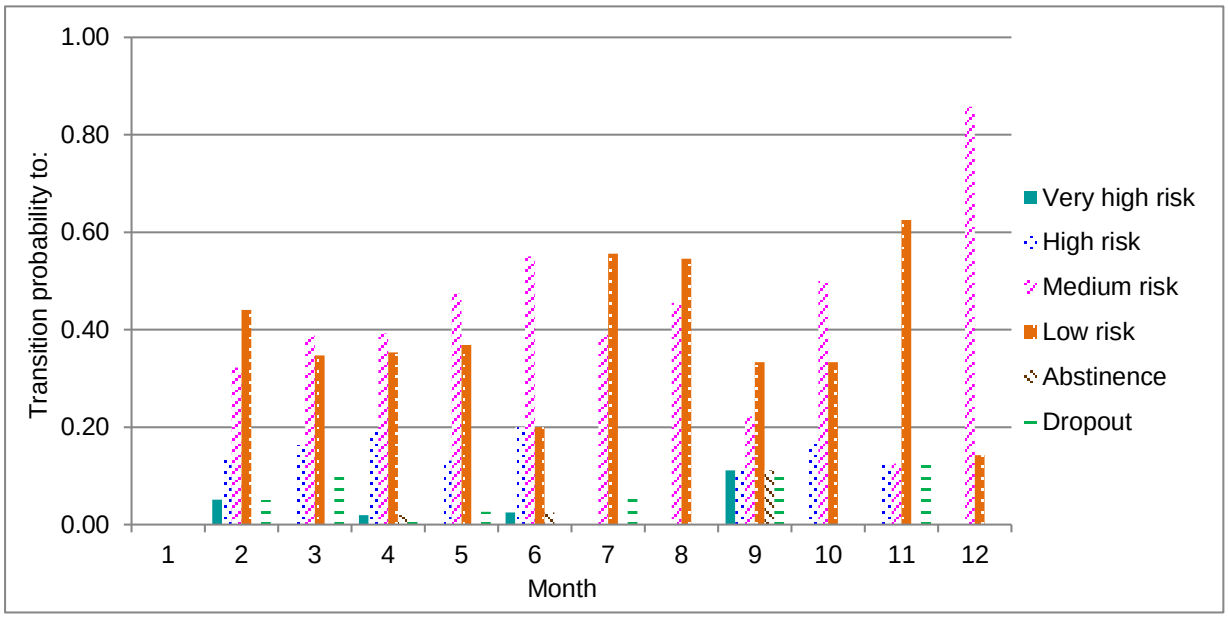


a) PI and nalmefene treated patients

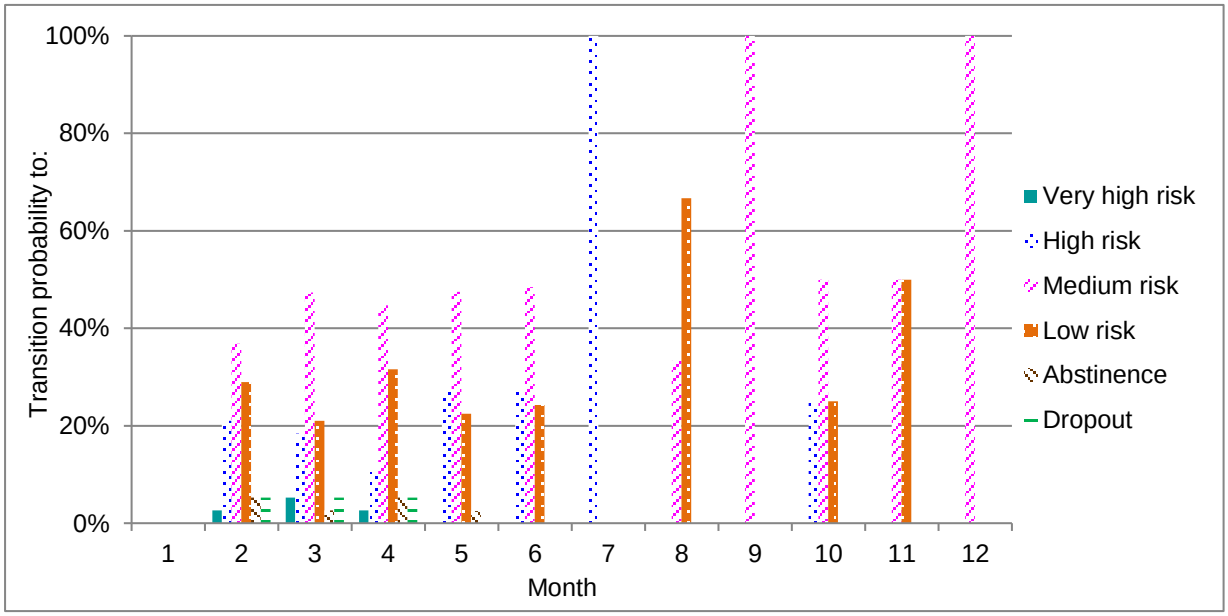


b) PI treated patients

Figure 10: Transition probabilities assumed in the model in the first year from medium-risk drinking levels

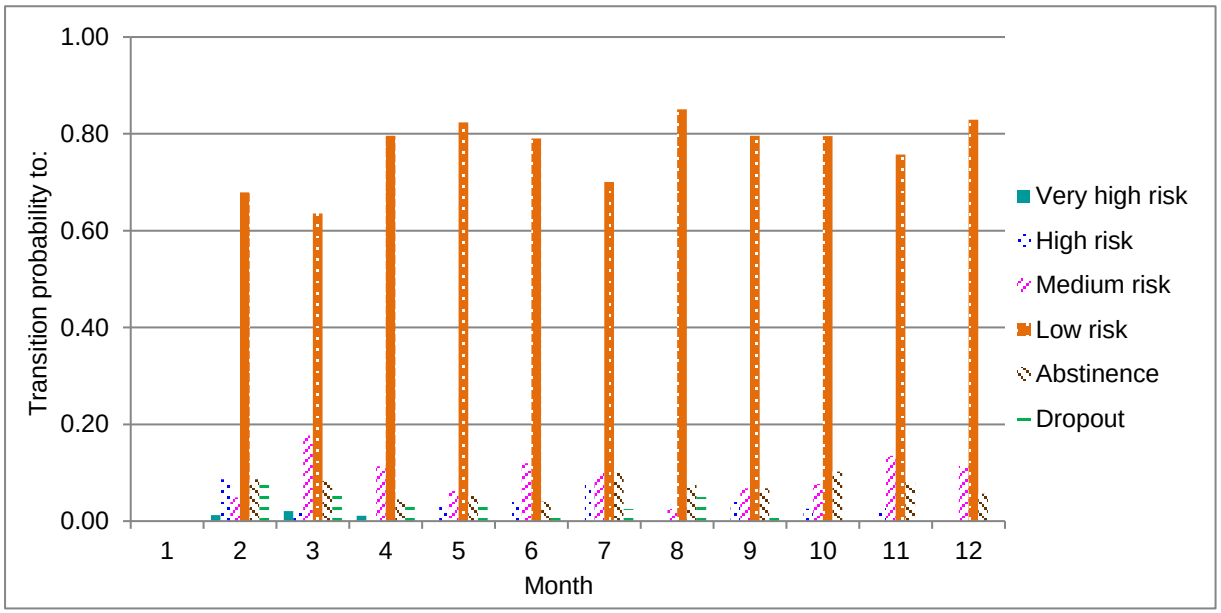


a) PI and nalmefene treated patients

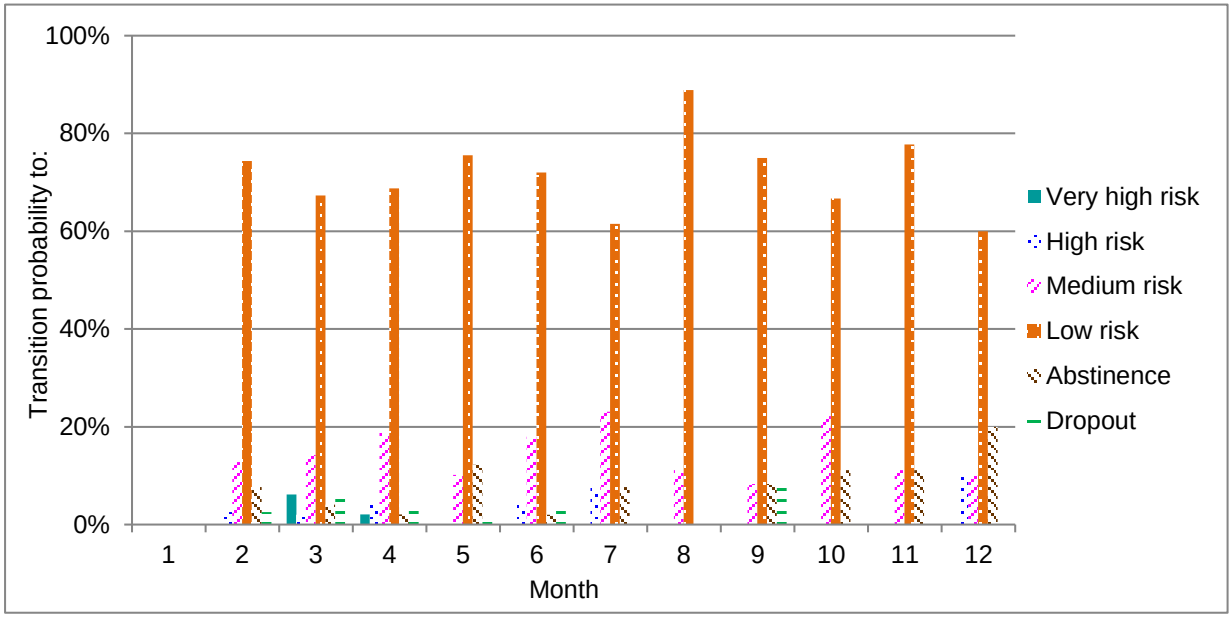


b) PI treated patients

Figure 11: Transition probabilities assumed in the model in the first year from low-risk drinking levels

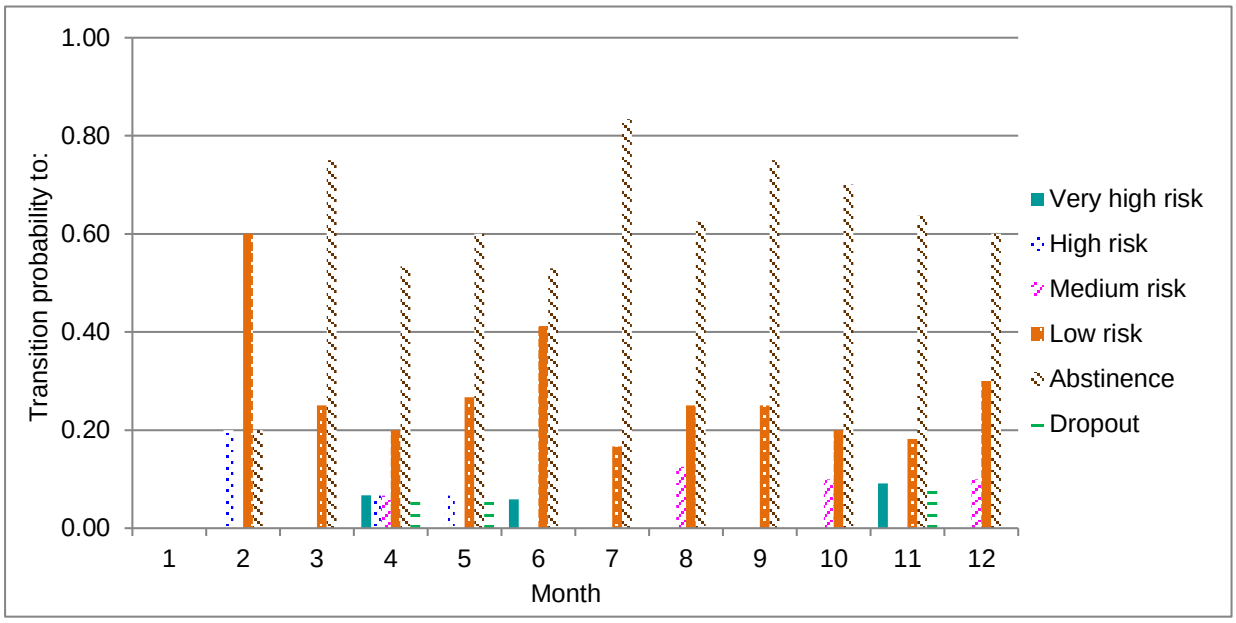


a) PI and nalmefene treated patients

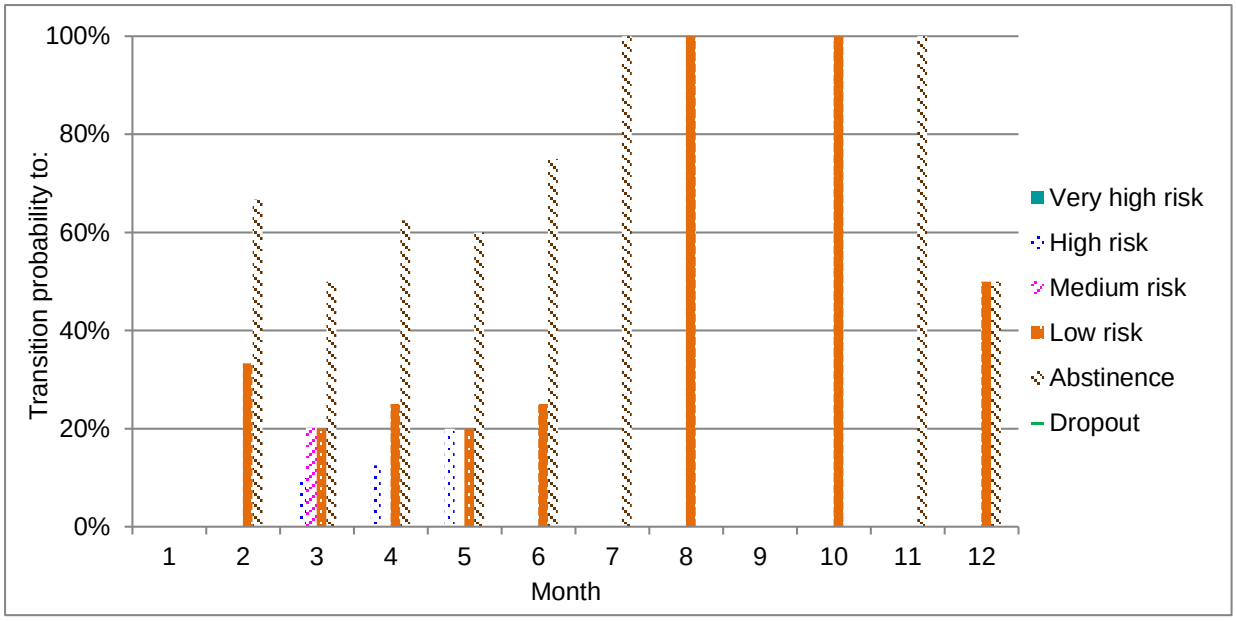


b) PI treated patients

Figure 12: Transition probabilities assumed in the model in the first year from abstinence



a) PI and nalmefene treated patients



b) PI treated patients

5.2.5.2 The risks of serious or temporary events in subsequent years

The assumed risks of experiencing a serious event or a temporary event are shown in Table 18 for men and Table 19 for women. Note that patients who have already experienced a serious event cannot have a second serious event and in such cases the transition probabilities would be set to 0%. The ERG believes that there has been an overestimation of the number of events and that the abstinent risk should be lower than the general population level in order that the weighted average equals that for the general population. An example of this would be for ischemic heart disease where the relative risk for those in the low-, medium-, high-, and very high-risk drinking levels are 2.66 compared with the general population, whilst the relative risk is 1 in the abstinent group. However, if this error is present the impact is likely to be slight, albeit favourable to nalmefene.

Table 18: Probability of serious or temporary events occurring in the first year of treatment for men

Description	Drinking risk level				
	Very high	High	Medium	Low	Abstinence
Heart disease	0.14%	0.12%	0.09%	0.07%	0.05%
Ischaemic stroke	0.03%	0.02%	0.02%	0.01%	0.01%
Haemorrhagic stroke	0.01%	0.01%	0.01%	0.00%	0.00%
Cirrhosis of the Liver	0.04%	0.02%	0.01%	0.01%	0.00%
Pancreatitis	0.07%	0.01%	0.01%	0.00%	0.00%
Lower respiratory infection	0.09%	0.07%	0.06%	0.05%	0.05%
Injury associated with transport	0.12%	0.09%	0.05%	0.00%	0.00%
Injury not associated with transport	0.58%	0.44%	0.24%	0.08%	0.02%

Table 19: Probability of serious or temporary events occurring in the first year of treatment for women

Description	Drinking risk level				
	Very high	High	Medium	Low	Abstinence
Heart disease	0.06%	0.04%	0.03%	0.03%	0.00%
Ischaemic stroke	0.02%	0.02%	0.01%	0.01%	0.00%
Haemorrhagic stroke	0.00%	0.00%	0.00%	0.00%	0.00%
Cirrhosis of the Liver	0.00%	0.00%	0.00%	0.00%	0.00%
Pancreatitis	0.00%	0.00%	0.00%	0.00%	0.00%
Lower respiratory infection	0.07%	0.05%	0.05%	0.05%	0.04%
Injury associated with transport	0.08%	0.03%	0.01%	0.00%	0.00%
Injury not associated with transport	0.56%	0.28%	0.14%	0.05%	0.02%

5.2.5.3 The risks of crime in the first year of treatment

The manufacturer applies relative risks for each drinking risk level to an underlying general population value, which is assumed to apply to those patients that are abstinent. The ERG believes that there has been an overestimation of the number of events and that the abstinent risk should be lower than the general population level in order that the weighted average equals that for the general population. However, if this error is present the impact is likely to be slight, albeit favourable to nalmefene. The assumed probabilities of committing crime by gender in the first year are provided in Table 20 for men and Table 21 for women. The probability for theft from shops appeared high at 84% for men, however, the ERG checked the calculations performed and assumes that the probability is high due to large numbers of repeat offenders within a year.

Table 20: The assumed probability of committing crime in first year of treatment by drinking level for men

Description	General population risk	Relative risk compared with general population risk			
		Very high-risk	High-risk	Medium-risk	Low risk
Causing death by dangerous driving	0.001%	4.55	3.38	3.20	2.45
More serious wounding	0.089%	3.48	2.66	2.54	2.01
Less serious wounding	10.720%	3.48	2.66	2.54	2.01
Assault on a constable	0.478%	5.40	3.95	3.74	2.80
Assault without injury	4.554%	5.40	3.95	3.74	2.80
Criminal damage	13.088%	10.04	7.06	6.62	4.69
Theft from a person	1.292%	1.20	1.14	1.13	1.08
Robbery	1.016%	1.20	1.14	1.13	1.08
Robbery (business)	0.095%	1.20	1.14	1.13	1.08
Burglary in a dwelling	1.914%	1.20	1.14	1.13	1.08
Burglary not in a dwelling	2.062%	1.20	1.14	1.13	1.08
Theft of a pedal cycle	0.973%	1.20	1.14	1.13	1.08
Theft from vehicle	3.441%	2.04	1.70	1.65	1.43
Aggravated vehicle taking	0.032%	2.04	1.70	1.65	1.43
Theft of vehicle	0.535%	2.04	1.70	1.65	1.43
Other theft	3.543%	1.20	1.14	1.13	1.08
Theft from shops	84.053%	1.20	1.14	1.13	1.08
Violent disorder	0.009%	4.55	3.38	3.20	2.45
Sexual offences	1.049%	4.55	3.38	3.20	2.45
Homicide	0.004%	4.55	3.38	3.20	2.45

Table 21: The assumed probability of committing crime in first year of treatment by drinking level for women

Description	General population risk	Relative risk compared with general population risk			
		Very high-risk	High-risk	Medium-risk	Low risk
Causing death by dangerous driving	0.000%	5.64	4.28	3.85	2.70
More serious wounding	0.014%	9.19	5.82	5.18	3.50
Less serious wounding	1.747%	9.19	5.82	5.18	3.50
Assault on a constable	0.078%	4.70	3.18	2.89	2.13
Assault without injury	0.742%	4.70	3.18	2.89	2.13
Criminal damage	1.325%	11.83	7.38	6.53	4.30
Theft from a person	0.437%	1.23	1.14	1.12	1.07
Robbery	0.053%	1.23	1.14	1.12	1.07
Robbery (business)	0.005%	1.23	1.14	1.12	1.07
Burglary in a dwelling	0.104%	1.23	1.14	1.12	1.07
Burglary not in a dwelling	0.112%	1.23	1.14	1.12	1.07
Theft of a pedal cycle	0.329%	1.23	1.14	1.12	1.07
Theft from vehicle	1.164%	22.82	13.85	12.13	7.66
Aggravated vehicle taking	0.011%	22.82	13.85	12.13	7.66
Theft of vehicle	0.181%	22.82	13.85	12.13	7.66
Other theft	1.199%	1.23	1.14	1.12	1.07
Theft from shops	13.696%	1.23	1.14	1.12	1.07
Violent disorder	0.001%	6.58	4.28	3.85	2.70
Sexual offences	0.000%	6.58	4.28	3.85	2.70
Homicide	0.001%	6.58	4.28	3.85	2.70

5.2.6 Transition probabilities in subsequent years

5.2.6.1 Transitions among drinking risk levels in subsequent years

Transition probabilities for those in the abstinent or low risk drinking levels are based on data reported by Taylor *et al*.[76] although the ERG notes that these data were collected 30 years ago and thus there may be uncertainty in the generalisability of these data to 2014. The estimated value of relapse from abstinence / low-risk drinking level was 19%, with the manufacturer assuming that all returned to the high- / very high-risk drinking levels in proportions of 42.5% and 57.5% respectively. These assumptions are potentially inaccurate for two reasons which influence the values in opposite directions i) Taylor *et al*.[76] state that 'It is necessary to emphasise that this analysis is based only on data obtained on 68 of the original 99 subjects…. If the tables which we give in the results section were read carelessly as a reflection of what happened to the total sample a far too optimistic impression would probably be gained. It must therefore be underlined that although methodologically this paper addresses general analytical problems related to alcoholism follow-up research, at the descriptive level it is dealing with a necessarily biased sample.': it appears that the manufacturer have used these data at face value and ii) that the possibility of patients regressing to the less severe social drinking state defined by Taylor *et al*. has been excluded. Therefore, it is unclear whether the assumption made by the manufacturer is favourable or unfavourable to nalmefene.

Transition probabilities for those in the medium-risk drinking level were calculated from the SENSE RCT with the MS stating that these 'were derived from the average transition probabilities of the medium-risk drinking level for the last 6 months of the SENSE 12-month trial'. If an average of the six values were actually used then this would cause inaccuracy where denominators change over time; however, the ERG cannot assess the impact this would have without access to the raw data. The transition probabilities in years 2 to 5 are shown in Table 22.

Table 22: The transition probabilities assumed from the medium-risk drinking level in years 2 to 5

	Nalmefene and PI		PI	
	Males	Females	Males	Females
To high- / very high-risk levels	9%	8%	16%	21%
To medium –risk level	42%	52%	26%	43%
To abstinence / low-risk levels	49%	40%	58%	36%

PI – Psychosocial Intervention

Transition probabilities for those in the high- / very high-risk drinking levels was estimated based on data within NICE CG115.[3] A network meta-analysis was undertaken in the guideline which indicated that the probability of relapse to heavy drinking at 12 months was 0.8176 (95% Credible Interval 0.3894 – 0.9996) for acamprosate and PI and 0.8253 (95% Credible Interval 0.4095 - 0.9997) for naltrexone and PI. In the MS it is stated that these values were similar, with the data for acamprosate and PI used in the modelling. The manufacturer states that based on clinical opinion, patients who relapse following treatment with naltrexone and PI or acamprosate and PI were assumed, each year, to have a 50% probability of having a further treatment round with naltrexone and PI / acamprosate and PI and 50% probability of remaining in the high / very high-risk drinking levels.

5.2.6.2 The risks of serious or temporary events in subsequent years

The annual risks of experiencing a serious or temporary event in years 2 to 5 are provided in Table 23 for men and 24 for women. Note that patients who have already experienced a serious event cannot have a second serious event and in such cases the transition probabilities would be set to 0%. The ERG believes that this assumption was made for reasons of simplicity and is likely to be unfavourable to nalmefene, although the impact is expected to be slight. As with the risks in the initial year it is believed that there has been an over-estimation of the number of serious and temporary events.

Table 23: Annual probability of serious or temporary events occurring following the first year of treatment for men

Description	Drinking risk level		
	Very high/High	Medium	Abstinent / Low Risk
Heart disease	1.66%	1.13%	0.83%
Ischaemic stroke	0.34%	0.23%	0.17%
Haemorrhagic stroke	0.11%	0.07%	0.05%
Cirrhosis of the Liver	0.32%	0.13%	0.07%
Pancreatitis	0.28%	0.08%	0.06%
Lower respiratory infection	0.93%	0.72%	0.61%
Injury associated with transport	1.44%	0.59%	0.02%
Injury not associated with transport	6.71%	3.11%	0.73%

Table 24: Annual probability of serious or temporary events occurring following the first year of treatment for women

Description	Drinking risk level		
	Very high/High	Medium	Abstinent / Low Risk
Heart disease	0.82%	0.55%	0.36%
Ischaemic stroke	0.34%	0.23%	0.15%
Haemorrhagic stroke	0.08%	0.04%	0.03%
Cirrhosis of the Liver	0.12%	0.07%	0.05%
Pancreatitis	0.09%	0.04%	0.04%
Lower respiratory infection	0.74%	0.60%	0.54%
Injury associated with transport	0.95%	0.15%	0.10%
Injury not associated with transport	5.44%	1.76%	0.50%

5.2.6.3 The probability of crime in subsequent years

As with the probability of crime in the first year the ERG believes that the number of events has been over-estimated. The assumed probabilities of committing crime by gender subsequent to the first year are provided in Table 25 for men and Table 26 for women.

Table 25: Annual probability of crime in years 2 to 5 for men

Description	General population risk	Relative risk given drinking risk level		
		Very high or high risk	Medium risk	Ex-drinkers
Causing death by dangerous driving	0.001%	3.94	3.20	1.99
More serious wounding	0.089%	3.05	2.54	1.69
Less serious wounding	10.720%	3.05	2.54	1.69
Assault on a constable	0.478%	4.65	3.74	2.23
Assault without injury	4.554%	4.65	3.74	2.23
Criminal damage	13.088%	8.49	6.62	3.52
Theft from a person	1.292%	1.17	1.13	1.06
Robbery	1.016%	1.17	1.13	1.06
Robbery (business)	0.095%	1.17	1.13	1.06
Burglary in a dwelling	1.914%	1.17	1.13	1.06
Burglary not in a dwelling	2.062%	1.17	1.13	1.06
Theft of a pedal cycle	0.973%	1.17	1.13	1.06
Theft from vehicle	3.441%	1.86	1.65	1.29
Aggravated vehicle taking	0.032%	1.86	1.65	1.29
Theft of vehicle	0.535%	1.86	1.65	1.29
Other theft	3.543%	1.17	1.13	1.06
Theft from shops	84.053%	1.17	1.13	1.06
Violent disorder	0.009%	3.94	3.20	1.99
Sexual offences	1.049%	3.94	3.20	1.99
Homicide	0.004%	3.94	3.20	1.99

Table 26: Annual probability of crime in years 2 to 5 for women

Description	General population risk	Relative risk given drinking risk level		
		Very high or high risk	Medium risk	Ex-drinkers
Causing death by dangerous driving	0.000%	5.59	3.85	2.07
More serious wounding	0.014%	7.74	5.18	2.57
Less serious wounding	1.747%	7.74	5.18	2.57
Assault on a constable	0.078%	4.05	2.89	1.71
Assault without injury	0.742%	4.05	2.89	1.71
Criminal damage	1.325%	9.91	6.53	3.08
Theft from a person	0.437%	1.19	1.12	1.04
Robbery	0.053%	1.19	1.12	1.04
Robbery (business)	0.005%	1.19	1.12	1.04
Burglary in a dwelling	0.104%	1.19	1.12	1.04
Burglary not in a dwelling	0.112%	1.19	1.12	1.04
Theft of a pedal cycle	0.329%	1.19	1.12	1.04
Theft from vehicle	1.164%	18.96	12.13	5.19
Aggravated vehicle taking	0.011%	18.96	12.13	5.19
Theft of vehicle	0.181%	18.96	12.13	5.19
Other theft	1.199%	1.19	1.12	1.04
Theft from shops	13.696%	1.00	1.00	1.00
Violent disorder	0.001%	5.59	3.85	2.07
Sexual offences	0.000%	5.59	3.85	2.07
Homicide	0.001%	5.59	3.85	2.07

5.2.7 Costs

5.2.7.1 Costs of the intervention and comparator

In the ESENSE1, ESENSE2 and SENSE RCTs patients in both arms had three appointments either with their GP or at a specialist care centre in the first month of treatment. Thereafter patients receiving nalmefene plus PI and those receiving PI alone had one appointment per month. The manufacturer used costs reported by the Personal Social Services Research Unit of £63 for an appointment with a GP, based on 17.2 minutes per appointment, and £94 for the cost of an appointment at a specialist care drug and alcohol service centre.[77] The manufacturer stated that 'Clinical experts advised the manufacturer that 75% of patients would be treated at a GP practice with the remainder treated at a specialist care centre'. However, this assumption is not supported by the clinical advisors to the ERG, who stated that in best practice a greater proportion would be treated in specialist care centres. The

manufacturer estimated that the undiscounted costs of PI alone for a person who does not drop out would be 14 x (£63 x 0.75 + £94 x 0.25) or £991 per annum, although the total would be greater if a larger proportion of patients were treated in specialist care centres. More recent costs, using a different methodology than those used by the manufacturer have been reported by the Personal Social Services Research Unit. The cost of a face-to-face contact with a specialist prescriber for drug misuse is reported to be £119 and has been used by the ERG in sensitivity analyses.[78]

The manufacturer states that 'The Department of Health has approved a UK nalmefene price of £3.03 per tablet', which if the drug is taken every day would add an additional £1107 per annum. The manufacturer states that in 'the pivotal clinical trials, the observed case analysis showed that patients took medication an average of 127 days per annum. With a cost per patient based on nalmefene costing £3.03 per tablet, the average cost of nalmefene would be £385 per year. According to the primary statistical mixed model repeated measures analysis, patients took medication on an average of 56% of days (204 days),' which the ERG has calculated would be a cost of £620 per year of nalmefene. Drug wastage, by not completing a full pack, was not explicitly included by the manufacturer although a scenario analysis was undertaken in which nalmefene was assumed to be taken every day rather than as required. No monitoring costs, for example increased liver function tests, were included in the model, although the clinical advisors to the ERG did not see this as a large limitation given the low price of such tests, and that only a small proportion of patients would receive these in the nalmefene plus PI arm, but not in the PI arm alone.

Superseded – see Erratum

Within the mathematical model the average nalmefene use per month was subdivided into sex and drinking risk levels. These data are replicated in Table 27. The ERG comments that those patients in the abstinent group were still taking nalmefene tablets which may be contrary to the nalmefene SPC which states that 'If you and your doctor have decided that your immediate goal is abstinence (not drinking any alcohol), you should not take Selincro because Selincro is indicated for reduction of alcohol consumption'.[14]

Table 27: Average nalmefene intake per month by sex and drinking risk level

	Average Intake per month (20mg tablets)	
Drinking Risk Level	Males	Females
Very High	20.47	19.12
High	19.89	18.89
Medium	16.54	16.46
Low	13.92	14.82
Abstinent	8.80	7.71

5.2.7.2 Costs of medically assisted withdrawal

The manufacturer assumed that 12.5% of patients received inpatient medically assisted withdrawal, 43.75% received outpatient medically assisted withdrawal and 43.75% received home-based medically assisted withdrawal (see NICE CG115 for definitions). The costs assumed by the manufacturer were taken (and assumed to remain at 2009/10 prices) from NICE CG115[3] which were between £4145 and £6175 for each patient receiving inpatient medically assisted withdrawal, £606 for each patient receiving outpatient medically assisted withdrawal, and between £596 and £771 for those receiving home-based medically assisted withdrawal. The manufacturer used the lower estimate of the range in both instances which is unfavourable to nalmefene, producing a weighted average of £1404 per patient receiving medically assisted withdrawal.

The proportion of patients receiving medically assisted withdrawal as an inpatient was thought to be too high by the clinical advisors to the ERG given the characteristics of the population entering the model; if this was the case then the assumptions made by the manufacturer would be favourable to nalmefene.

Superseded – see Erratum

5.2.7.3 Costs of serious and temporary events

The costs for serious and temporary events were stated as being largely taken from a report written by the University of Sheffield.[75] Distributions on these costs were estimated assuming that the standard error was 20% of the mean. The one exception was the costs of lower respiratory infection, which was not included in the University of Sheffield report. These data were stated to be taken from NHS Reference Costs, with a distribution estimated assuming that the standard error was 20% of the mean, although no reference was provided to check the mean values. All prices were inflated to 2011/2012.[77] These data are reproduced in Table 28.

However, there appear to be a number of discrepancies between the values reported by the manufacturer and the values reported in the University of Sheffield report.[79] The reasons for the discrepancies are unknown but it is noted that most of the manufacturer's values were unfavourable to nalmefene. The uninflated University of Sheffield values have been detailed in Table 28. These costs are stated to be 'Total cost per person-specific hospitalisation' and thus ongoing costs, for example for patients who have had a stroke, are not considered. This omission is likely to be unfavourable to nalmefene.

Table 28: Costs associated with adverse events used by the manufacturer

Event	Mean value used in the model	Distribution used in the model	Distribution parameters used in the model	Uninflated value in the University of Sheffield report.[79] (Appendix 5)
Heart disease	£2,491	Gamma	α = 25 ß = 99.658	£4,572
Ischaemic stroke	£4,088	Gamma	α = 25 ß = 163.525	£7,502
Haemorrhagic stroke	£5,799	Gamma	α = 25 ß = 231.956	£5,738
Cirrhosis of the liver	£3,750	Gamma	α = 25 ß = 150.008	£4,626[a]
Pancreatitis	£4,373	Gamma	α = 25 ß = 174.903	£19,324
Lower respiratory infection	£2,999	Gamma	α = 25 ß = 119.974	N/A
Injury associated with transport	£5,468	Gamma	α = 25 ß = 218.733	£14,382[b]
Injury not associated with transport	£5,296	Gamma	α = 25 ß = 211.84	£4,225[c]

[a] Assumed to be alcoholic liver disease [b] Assumed to be road traffic accidents - non pedestrian

[c] Assumed to be Fall injuries N/A – Not available

Superseded – see Erratum

5.2.7.4 The costs of crime

The costs of the set of crimes that are an option for inclusion in the model are detailed in Table 29, which replicates Table B65 on p225 of the MS. These values have been calculated with monetary values placed on the lost health gains. As such only costs are included in the model with no further health decrement modelled. The validity of this method has been questioned by Rittenhouse[80] where the ICERs estimated when health effects are monetised and included in the numerator rather than transformed into QALYs and included in the denominator.

Table 29: The unit costs of crime assumed in the model

Crime	**Cost**
Causing death by dangerous driving	£1,794,890
More serious wounding	£26,354
Less serious wounding	£9,911
Assault on a constable	£1,772
Assault without injury	£1,772
Criminal damage	£1,065
Theft from a person	£1,038
Robbery	£8,959
Robbery (business)	£6,151
Burglary in a dwelling	£4,020
Burglary not in a dwelling	£3,322
Theft of a pedal cycle	£780
Theft from vehicle	£1,056
Aggravated vehicle taking	£5,091
Theft of vehicle	£5,091
Other theft	£780
Theft from shops	£123
Violent disorder	£12,803
Sexual offences	£38,676
Homicide	£1,794,890

Superseded – see Erratum

5.2.8 Utilities

5.2.8.1 Utilities associated with drinking risk levels in the first year

The utility associated with each drinking risk level were obtained from EQ-5D questionnaire administered in the three RCTs (ESENSE1[28], ESENSE2[31], SENSE[32]). In two of these trials (ESENSE1, ESENSE2) the EQ-5D questionnaire were administered at baseline, week 12 and week 24 and in the remaining trial (SENSE) EQ-5D questionnaires were administered at baseline, week 12, week 25, week 36 and week 52.

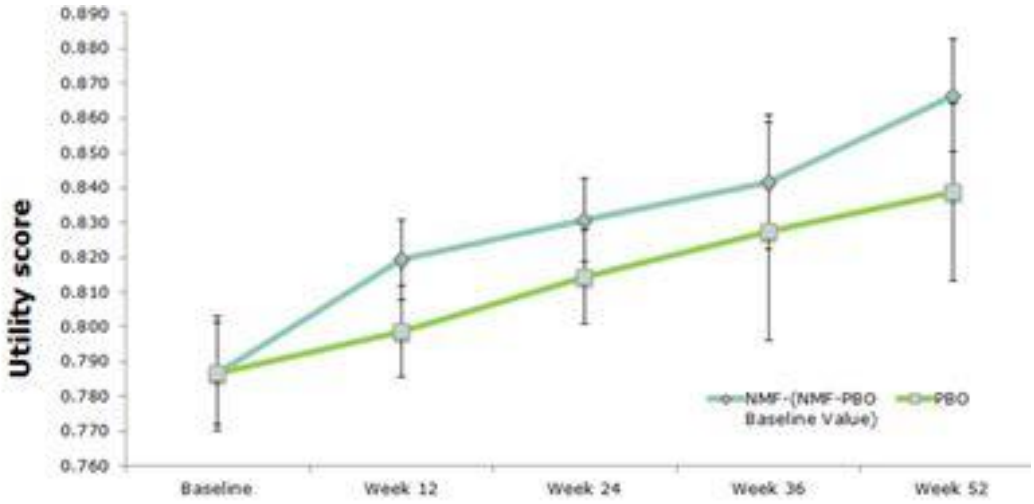
The area under the curve was estimated at every three months from baseline to one year (adjusted for the baseline utility, and assuming a linear transition between the mean utilities at each time point). The manufacturer states in response to clarification question C5 that "this method of applying utilities from a clinical trial was informed by NICE CG115 and has the advantage of being able to capture the disutility of adverse events relating to nalmefene." However, this approach may have limitations since data from people who dropped out, or data that was otherwise missing, were not imputed, as stated in the manufacturer's response to clarification question C6. Given the relative frequency of dropout the

lack of imputation may be favourable to nalmefene in Figure 13, although within the model this bias would likely be removed as set utility values per drinking-risk level are used.

Superseded – see Erratum

The manufacturer provided a graph of mean utility values recorded within the ESENSE1[28], ESENSE2[31], and SENSE[32] RCTs (Figure B23, page 208 of the MS). This is reproduced in Figure 13.

Figure 13: Mean utility values associated with treatment in the first year: pooled data from ESENSE1, ESENSE2 and SENSE



NMF = nalmefene; PBO = placebo

The ERG notes that within the probabilistic sensitivity analyses (PSA) the mean and standard errors are used to form beta distributions. Sampling from these beta distributions produces more uncertainty than seen in Figure 13 which is likely to be marginally unfavourable to nalmefene.

5.2.8.2 Utilities associated with drinking risk levels after the first year

In years 2 to 5 the manufacturer assumed that utility was unaffected by the initial treatment given to the patient, although the ERG notes that this may introduce inaccuracy if patients with a medium-risk drinking level are assumed to be maintained on treatment. The base case analysis used pooled data from ESENSE1, ESENSE2 and SENSE. These values are provided in Table 30. As expected, the more severe the drinking risk level, the lower the estimated utility.

Table 30: Utility data derived from the ESENSE1, ESENSE2 and SENSE RCTs

Description	Mean value	Distribution	Parameters
Utility associated with drinking risk levels			
Very high or high	0.79	Beta	α = 1310 ß = 348
Medium	0.82	Beta	α = 1210 ß = 266
Low or abstinent	0.86	Beta	α = 1035 ß = 168

An alternative source was also considered for estimating utility data. These were from a naturalistic disease management study (STREAM study) of patients with alcohol dependence in the UK primary care setting at the GP level.[81] These values are provided in Table 31 and have lower midpoint utility levels per drinking risk level than in the base case, and also greater uncertainty in the values.

Superseded – see Erratum

Table 31: Utility data derived from the STREAM RCT

Description	Mean value	Distribution	Parameters
Utility associated with drinking risk levels			
Very high	0.531	Beta	α = 65 ß = 57
High	0.609	Beta	α = 74 ß = 48
Medium	0.714	Beta	α = 53 ß = 21
Medium	0.755	Beta	α = 96 ß = 31
Low or abstinent	0.816	Beta	α = 40 ß = 9

5.2.8.3 Utilities associated with serious and temporary events

The utility values associated with each serious or temporary event are detailed in Table 32. All values were taken from a report undertaken by the University of Sheffield.[79] The original source did not assume uncertainty in these values, and in order to include these variables within PSA the manufacturer assumed a standard error of the mean of 0.02 and fitted a beta distribution to the values.

Table 32: Utility values associated with serious and temporary events used by the manufacturer

Description	Mean value	Distribution	Parameters
Utility, general population	0.85	Beta	α = 164 ß = 28
Utility, heart disease	0.64	Beta	α = 368 ß = 204
Utility, ischaemic stroke	0.56	Beta	α = 346 ß = 267
Utility, haemorrhagic stroke	0.66	Beta	α = 369 ß = 193
Utility, cirrhosis of the liver	0.49	Beta	α = 308 ß = 315
Utility, pancreatitis	0.45	Beta	α = 276 ß = 341
Utility, lower respiratory infection	0.20	Beta	α = 80 ß = 320
Utility, injury associated with transport	0.60	Beta	α = 359 ß =241
Utility, injury not associated with transport	0.59	Beta	α = 357 ß = 246

5.2.9 Results

5.2.9.1 Results from the manufacturer's base case analysis

The manufacturer's base case included the following key assumptions, which were relaxed in scenario analyses:

- A time horizon of five years
- Nalmefene, taken as needed, in addition to PI
- Second line treatment with naltrexone and acamprosate modelled
- Direct NHS and PSS costs only
- Utility data derived from the ESENSE1, ESENSE2 and SENSE RCTs

The manufacturer provided a graphical representation of the simulated drinking risk levels for those receiving PI and for those receiving nalmefene and PI. These representations (Figure B25 and Figure B26 in the MS) are reproduced in Figures 14 and 15. The ERG believes that those patients not within a drinking state comprise those simulated to have died, or those who have sustained a serious event. The results show a less harmful drinking profile for those on nalmefene and PI.

Figure 14: The proportion of patients in each drinking level of those patients receiving PI in the initial year

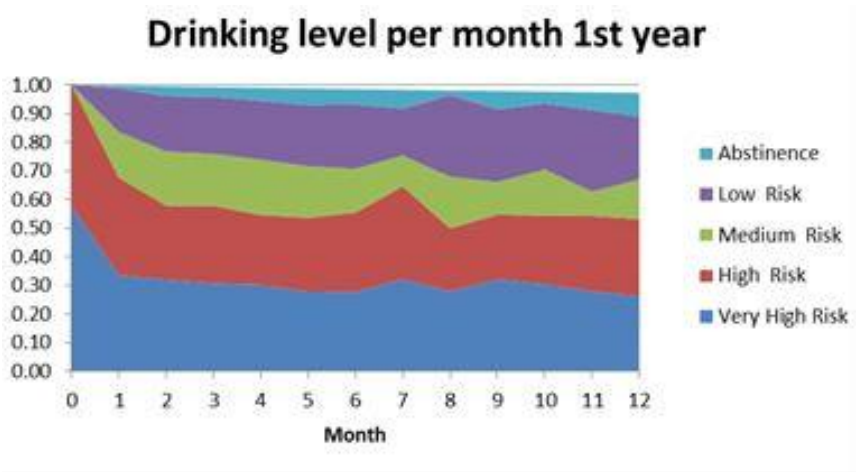
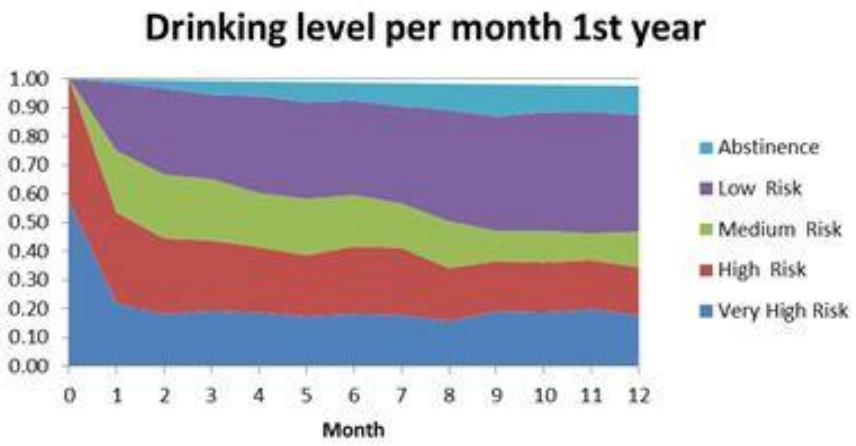


Figure 15: The proportion of patients in each drinking level of those patients receiving nalmefene and PI in the initial year



The proportion of patients in each drinking risk level over the five year time horizon for PI treatment and nalmefene and PI treatment were included in the MS (Figures B70 and B71 on page 235). These have been reproduced in Tables 33 and 34 and show a sustained improvement for those receiving nalmefene in addition to PI.

Table 33: The proportion of patients in each drinking level of those patients receiving PI in the five year time horizon

	Year 1	Year 2	Year 3	Year 4	Year 5
Very high risk	26.3%	44.7%	42.3%	40.7%	39.2%
High risk	26.8%				
Medium risk	13.9%	8.3%	6.0%	4.9%	4.3%
Low risk	21.9%	42.4%	44.4%	44.7%	44.3%
Abstinence	8.4%				
Death[a]	0.9%	1.6%	2.5%	3.3%	4.2%
Serious events[b]	1.7%	3.0%	4.7%	6.4%	7.9%
Temporary events[c]	5.4%	1.4%	4.2%	3.8%	3.6%

[a] Deaths due to both all-cause mortality and harmful events.

[b] Only serious harmful events that make the patient stop drinking.

[c] These patients are still drinking and thus double counted in this table, as they are included in both the drinking health state and the temporary events.

Table 34: The proportion of patients in each drinking level of those patients receiving nalmefene plus PI in the five year time horizon

	Year 1	Year 2	Year 3	Year 4	Year 5
Very high risk	17.8%	28.7%	27.1%	26.0%	25.1%
High risk	16.7%				
Medium risk	12.5%	7.3%	5.4%	4.5%	4.1%
Low risk	40.5%	59.7%	60.9%	60.6%	59.7%
Abstinence	10.2%				
Death[a]	0.8%	1.5%	2.3%	3.1%	3.9%
Serious events[b]	1.5%	2.8%	4.4%	5.8%	7.3%
Temporary events[c]	4.4%	1.4%	3.1%	2.8%	2.7%

[a] Deaths due to both all-cause mortality and harmful events.

[b] Only serious harmful events that make the patient stop drinking.

[c] These patients are still drinking and thus double counted in this table, as they are included in both the drinking health state and the temporary events.

The numbers of adverse events in each arm were reported in the MS (Table B69, p233). These are reproduced in Table 35 and are per 100,000 patients.

Table 35: The estimated number of serious and temporary events in the base case per 100,000 patients

	Nalmefene + PI	PI	Difference (PI − nalmefene + PI)
Ischaemic heart disease	4,092	4,446	354
Ischaemic stroke	977	1,068	92
Haemorrhagic stroke	287	314	26
Liver cirrhosis	568	672	104
Pancreatitis	517	630	113
Lower respiratory tract infections	2,418	2,728	310
Transport injuries	1,665	2,341	676
Injuries other than transport	9,950	13,133	3,183
Deaths from serious events	1,945	2,195	250
Deaths from short-term events	557	634	77
Number of events	20,474	25,331	4,857
Number of deaths	1,945	2,195	250

The base case deterministic cost and QALY results are reproduced in Table 36. The manufacturer has provided additional disaggregated results in the MS, although for brevity these are not reported here.

Table 36: Base case deterministic results presented by the manufacturer

Treatment	Total costs	Total QALYs	Incremental costs	Incremental OALYs	ICER
PI	£4,842	3.553			
Nalmefene + PI	£4,445	3.624	-£397	0.071	Dominating

PSA was undertaken with the results provided in Table 37. These were generated from 5000 sample configurations. The manufacturer used non-informative priors (of 0.1) to facilitate the derivation of beta distributions for transition probabilities where there were zero observed counts. A slight error was noted in the PSA analysis regarding the population of the percentage of patients who would be treated by a GP as the deterministic value was 75%, however, the probabilistic distribution was uniform between 40% and 60%. Amending this distribution to a uniform (65%, 85%) made little difference to the results and therefore for transparency reasons the results presented in the MS rather than amended results have been reported in Table 37.

Superseded – see Erratum

The ERG comment that in the manufacturer's base case there are more unfavourable assumptions to nalmefene than favourable assumptions, although the magnitude of these assumptions combined are unknown. Unfavourable assumptions included: underestimation of the costs of serious and temporary events due to the omission of ongoing costs; a time horizon of 5 years, the assumption that age and gender matched mortality rates are applicable to the population in the decision problem and those that have had a serious or temporary event; that only one serious event was permitted; that drinking risk levels were considered irrelevant after a serious event; using the lower bounds and uninflated costs of costs of a medically assisted withdrawal. The favourable assumptions to nalmefene included: over-estimation of rates of serious and temporary events; the over-estimation of crime rates; the high (in the opinion of the clinical advisors to the ERG) proportion of patients receiving medically assisted withdrawal as an inpatient; the assumption that all patients would require medically assisted withdrawal if they remained at high- or very high- risk levels at 12 months; that drug wastage was not included in the base case; and the fact that nalmefene-related adverse events were not incorporated in terms of costs and disutility.

Table 37: Base case probabilistic results presented by the manufacturer

Treatment	Total costs	Total QALYs	Incremental costs	Incremental OALYs	ICER
PI	£5,220	3.535			
Nalmefene + PI	£4,760	3.621	-£460	0.087	Dominating

It is seen that the PSA results were more favourable to nalmefene than the deterministic results producing greater cost savings and greater QALYs. For completeness, the cost-effectiveness scatter plot and cost-effectiveness acceptability curve generated by the PSA are reproduced in Figures 16 and 17.

Figure 16: The cost-effectiveness scatter plot presented by the manufacturer

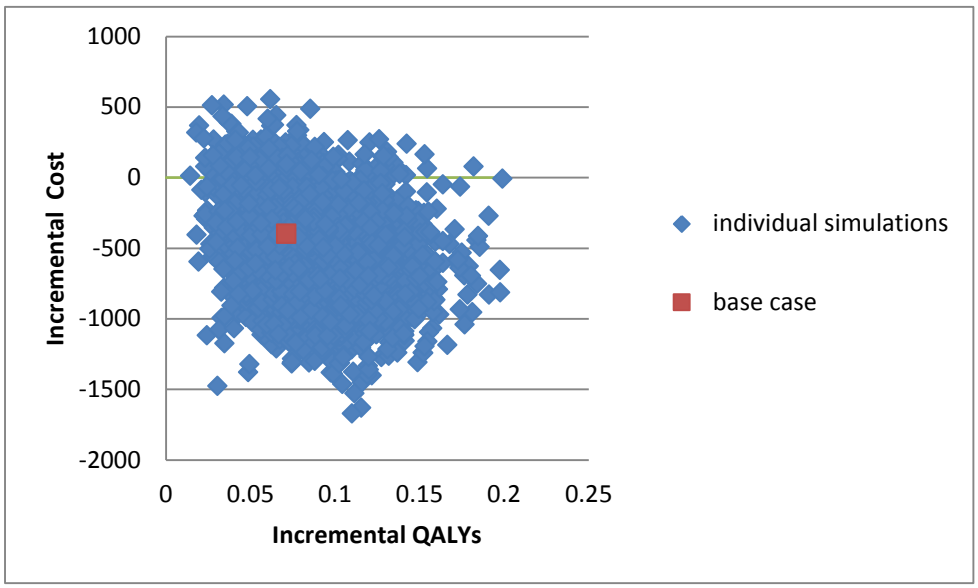
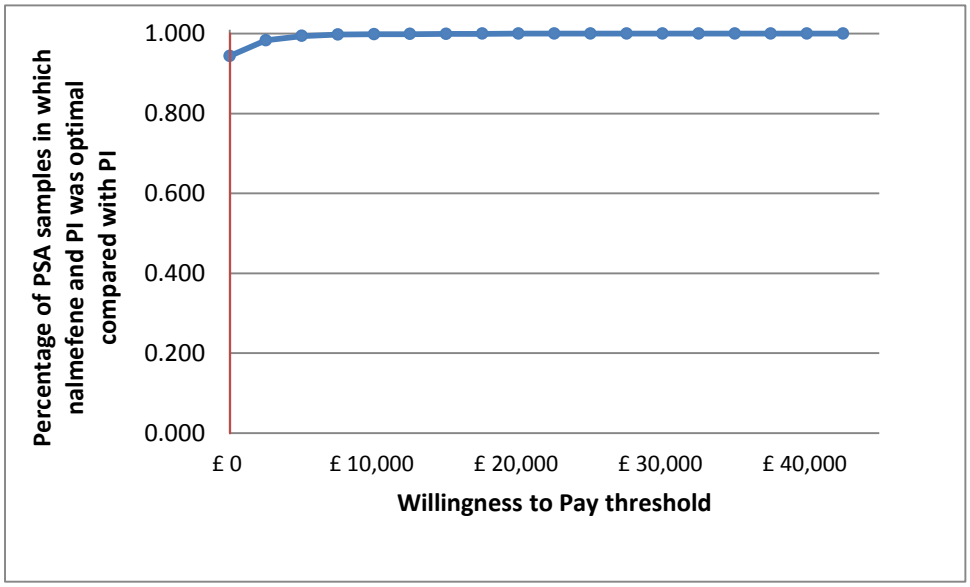


Figure 17: The cost-effectiveness acceptability curve presented by the manufacturer



Given the relative similarity between the probabilistic and deterministic results the manufacturer presented further results (one way sensitivity analyses and scenario analyses) using the deterministic model.

5.2.9.2 One way sensitivity analyses

The manufacturer presented such results in Table B80 (page 240) of the MS. These are reproduced in Table 38. It is seen that none of the univariate sensitivity analyses materially altered the conclusions of the base case, and only in one univariate sensitivity analyses did nalmefene plus PI not dominate PI alone, where the medical visits per month associated with nalmefene was doubled.

Table 38: Univariate sensitivity analyses presented by the manufacturer

Parameter	ICER at lower bound	ICER at upper bound	Mean value (range tested)
Medical visits per month nalmefene + PI	−£11,495	£6,274	1 (0.5-2)
Medical visits per month for PI treatment	−£425	−£15,867	1 (0.5-2)
Utility – Area under the curve from ESENSE & SENSE PI	−£3,734	−£10,976	0.81 (0.77-0.85)
Utility – Area under the curve from ESENSE & SENSE nalmefene	−£8,561	−£4,130	0.83 (0.8-0.86)
Probability of relapse	−£7,652	−£3,682	0.19 (0.1-0.19)
Number of visits first month for nalmefene + PI treatment	−£8,083	−£4,317	3 (1-4)
Cost of nalmefene	−£7,316	−£3,829	3.03 (2.42-4)
Number of visits first month for PI treatment	−£3,331	−£6,693	3 (1-4)
QALY: abstinence	−£6,613	−£4,815	0.86 (0.84-0.86)
Discount rate: cost	−£6,666	−£4,898	4 (0-0.06)
Cost: other injury	−£4,740	−£6,405	5296.01 (3220.01-7372.05)
QALY: very high risk	−£4,894	−£6,469	0.79 (0.77-0.81)
Proportion of day at risk of other accidents (hours)	−£4,817	−£5,917	3 (1-4)
Cost of visit to GP	−£6,084	−£5,060	63 (38-87.7)
Discount rate: outcomes	−£5,028	−£5,975	3.5 (0-0.06)
Proportion of visits to GP (to specialized care)	−£4,929	−£5,786	0.75 (0-1)
Male RR other injury	−£5,281	−£6,030	2.19 (1.7-2.19)
Male RR mortality due to cirrhosis of the liver	−£5,737	−£5,125	1.69 (1.32-1.69)
Cost of follow-up attendance to specialized care	−£5,809	−£5,335	94 (57-131)
Female RR other injury	−£5,398	−£5,846	2.19 (1.7-2.19)
Base-case analysis	**−£5,574**		

GP = general practitioner; ICER = incremental cost-effectiveness ratio; PI = psychosocial intervention; QALY = quality-adjusted life-year; RR = relative risk.

5.2.9.3 Scenario analyses undertaken by the manufacturer

The manufacturer undertook eight scenario analyses. These are described below with explicit reference to the changes from the base case.

- Scenario 1: Time horizon reduced to 1 year
- Scenario 2: Societal perspective included
- Scenario 3: Time horizon reduced to 1 year and societal perspective included
- Scenario 4: Nalmefene intake assumed to be every day rather than as needed
- Scenario 5: No second-line treatment options are allowed
- Scenario 6: Using utility values from the STREAM study[81]
- Scenario 7: A threshold analysis increasing the treatment effect of PI relative to nalmefene in addition to PI to identify the level of efficacy required to have a cost per QALY of £20,000 and of £30,000.
- Scenario 8: An assumption that PI was associated with zero costs

Superseded – see Erratum

The results for these scenarios analyses (excluding Scenario 7) are shown in Table 39. This is essentially a replication of Table B81 (page 243 of the MS). The largest mean cost per QALY value generated in the scenario analyses was slightly below £25,000 and occurred when the modelling horizon was limited to a one year period. This is unfavourable to nalmefene and PI which resulted in more people being in less severe drinking states at month twelve, (as shown in Figure 14 and Figure 15), who would be assumed to generate no benefit in terms of health or savings. Four of the scenarios estimated that nalmefene would not be cost-saving. These scenarios include when medically assisted withdrawal was not allowed indicating that this has a marked effect of costs; the clinical advisors to the ERG thought that the present assumption that all patients received medically assisted withdrawal at 12 months if they were still in a high- or very high-risk level is unlikely to be correct.

The rationale for Scenario 8 is unclear, as nalmefene is only indicated to be prescribed in conjunction with continuous PI focused on treatment adherence and reducing alcohol consumption and the forms of PI recommended in NICE CG115[3] certainly incur costs. There is a presumed typographical error in Scenario 8 with respect to life years, which the ERG believes should be equal to those in Scenario 1. Furthermore the ERG could not replicate the cost results for Scenario 8, and it is unclear why there has been a much larger drop in the PI alone arm, despite PI being included in both arms.

The results from Scenario 7 are shown in Figure 18 which is a reproduction of Figure B29 on page 244 of the MS. This indicates that the efficacy difference between nalmefene and PI and PI alone

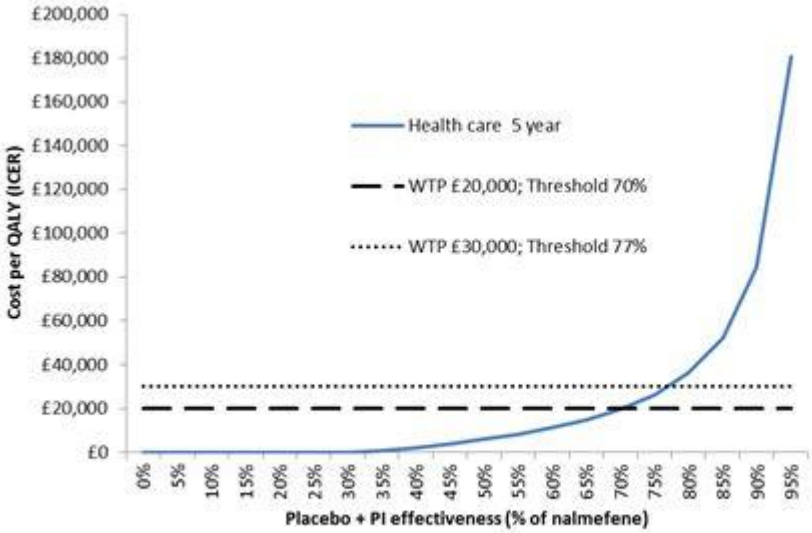
would need to be reduced by 70.3% for nalmefene and PI to have a cost per QALY of £20,000 and to be reduced by 77.2% for nalmefene in addition to PI to have a cost per QALY of £30,000. In the response to clarifications the manufacturer stated that they did not believe such a reduction was probable, although the clinical advisors to the ERG were less certain that a conclusion could be drawn.

Table 39: Scenario analyses results presented by the manufacturer (excluding scenario analysis 7)

Scenario Analysis	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/QALY (£)
	NMF + PI	PI	NMF + PI	PI	NMF + PI	PI				
Base-case analysis	£4,445	£4,842	4.413	4.404	3.624	3.553	-£397	0.009	0.071	Nalmefene + PI dominates
1	£1,571	£1,162	0.959	0.957	0.800	0.784	£408	0.002	0.017	£24,684
2	£15,632	£18,524	4.413	4.404	3.624	3.553	-£2,893	0.009	0.071	Nalmefene + PI dominates
3	£4,999	£5,094	0.959	0.957	0.800	0.784	-£95	0.002	0.017	Nalmefene + PI dominates
4	£4,863	£4,842	4.413	4.404	3.624	3.553	£21	0.009	0.071	£289
5	£2,959	£2,521	4.406	4.394	3.569	3.483	£438	0.012	0.086	£5,090
6	£4,445	£4,842	4.413	4.404	3.122	2.929	-£397	0.009	0.192	Nalmefene + PI dominates
8	£4,254	£3,678	3.624	3.553	3.624	3.553	£576	0.071	0.071	£8,088

LY = life-year; NMF = nalmefene; QALY = quality-adjusted life-year.

Figure 18: Results from Scenario Analysis 7



ICER = incremental cost-effectiveness ratio; PI = psychosocial intervention; QALY = quality-adjusted life-year; WTP willingness to pay.

Following the round of clarification questions the manufacturer amended a very minor logical error within the mathematical model (that made no material difference to the results) and presented a series of further scenario analyses. For continuity these are now termed 'Scenario Analysis 9' and 'Scenario Analysis 10'.

Scenario Analysis 9 attempted to provide an indicative ICER were the recommendations from NICE CG115 regarding PI put into practice and that there were one 60 minute session per week for 12 weeks which added additional costs for PI. Scenario A only increased the costs of PI, whereas Scenario B assumes that the increased costs of PI are also assumed to apply to the nalmefene and the PI arm. Table B within the second clarification response is reproduced in Table 40.

Table 40: Scenario analyses 9: assuming one 60 minute session per week for 12 weeks

Scenario	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
	NMF + PI	PI alone	NMF + PI	PI alone			
Base case	£4,445	£4,842	3.624	3.553	-£397	0.071	Nalmefene + PI dominates
Scenario A	£4,445	£5,933	3.624	3.553	-£1,488	0.071	Nalmefene + PI dominates
Scenario B	£4,874	£5,933	3.624	3.553	-£1,059	0.071	Nalmefene + PI dominates

NMF: Nalmefene; PI: Psychosocial Intervention

A major limitation of this analysis is that the manufacturer assumed that the effectiveness of PI, and nalmefene in addition to PI had the same efficacy as observed in the pivotal RCTs. The ERG believes that this limitation renders these analyses invalid, with the appropriate analysis being to use the increased costs of PI and undertake the threshold analysis as used in Scenario Analysis 7 of the MS. In addition, Scenario B appears to lack face validity with the costs of PI alone increasing markedly more than nalmefene plus PI.

The clinical advisors to the ERG were also concerned that Scenario A could be misinterpreted to suggest that the PI regime recommended in NICE CG115 was not necessary. This potential misinterpretation was supported by a comment from the manufacturer in the clarification response that "This highlights that treatment with nalmefene gives the option not only of adding a pharmacological treatment to psychosocial intervention as first-line treatment (post brief intervention), but also gives the option of providing a psychosocial intervention of a lower intensity - with motivational support that can be given in either primary or secondary care as part of a usual medical consultation." There is no evidence base for this statement.

Scenario Analysis 10 assessed alternative assumptions regarding the treatment pathway of those patients drinking to a medium-risk level after 12 months of treatment. Three scenarios were defined.

- Scenario A: Patients in the medium drinking health state are assumed to not have responded to treatment and relapse back to high/ very high DRL and thus change treatment strategy to an abstinence-orientated approach (second-line treatment option).

- Scenario B: Patients in the medium drinking health state are assumed to have responded to treatment and are modelled in line with other patients having responded to treatment in the controlled-drinking health state.

- Scenario C: An extreme scenario against nalmefene where patients in the medium drinking health state in the nalmefene plus PI arm are modelled to have not responded (as in Scenario A) and patients in the PI alone arm are modelled to have responded (as in Scenario B).

These results (provided in Table C of the clarification response) are reproduced in Table 41.

Table 41: Scenario analyses 10: altering the assumption of the treatment pathway of those drinking to a medium-risk level at 12 months

Scenario	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
	NMF + PI	PI alone	NMF + PI	PI alone			
Base case	£4,445	£4,842	3.624	3.553	-£397	0.071	Nalmefene + PI dominates
Scenario A	£4,803	£5,240	3.608	3.538	-£437	0.070	Nalmefene + PI dominates
Scenario B	£4,218	£4,559	3.638	3.570	-£341	0.068	Nalmefene + PI dominates
Scenario C	£4,803	£4,559	3.609	3.570	£244	0.039	£6,280/QALY
NMF: Nalmefene; PI: Psychosocial Intervention							

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG stresses that the decision problem cannot be fully evaluated with the currently available data. The ERG notes that four comparisons can be formulated and the ability to provide robust estimates of the cost-effectiveness of nalmefene in addition to PI decreases as the comparisons become more relevant to the decision problem

Comparison 1. A comparison of nalmefene plus PI being compared with PI alone with PI being approximated by BRENDA as used in the pivotal RCTs. This would not meet the decision problem specified in the final scope[70] as BRENDA is not equivalent to PI as recommended in CG115.

Comparison 2. A comparison of nalmefene plus PI being compared with PI alone with PI being that recommended in NICE CG115. A threshold analysis as performed by the manufacturer in Scenario Analysis 7, using the greater additional costs of such PI would provide some information on this comparison.

Comparison 3. A comparison of delayed addition of nalmefene use for those who did not respond to PI with immediate use of nalmefene in addition to PI; in both cases PI is that as recommended in NICE CG115. There are very limited data to allow such a comparison to be made, although the ERG note that even with the less intensive BRENDA that non-negligible proportions of patients transitioned from high- to low-risk and that additional costs of nalmefene may not be justified in all patients. The delayed addition of nalmefene would also be aligned with the recommendation for pharmacotherapy use in NICE CG115, although these were written before the licensing of nalmefene.

Comparison 4. A comparison of the delayed addition of nalmefene for those who did not respond to PI or immediate use of nalmefene in addition to PI versus the delayed addition of naltrexone in those

who did not respond to PI; in all cases PI is that as recommended in NICE CG115. The use of off-label naltrexone for 'people with mild alcohol dependence who have not responded to PI alone, or who have specifically requested a pharmacological intervention' is recommended in NICE CG115.

5.3.1 The exploratory ERG analyses in Comparison 1

The ERG undertook a number of exploratory analyses which are detailed below. These analyses are amendments of the manufacturer's base case except that it was assumed that those drinking to a medium-risk level at 12 months had relapsed to a high- / very high-risk level. (Scenario A of Scenario Analysis 10.)

Deterministic results are provided for each individual exploratory analysis. Probabilistic analyses were not undertaken although the ERG notes that this may be unfavourable to nalmefene based on the results provided in Table 42.

Superseded – see Erratum

The exploratory analyses conducted by the ERG are bulleted below. The results from the exploratory analyses undertaken are provided in Table 42.

- Alternative costs for serious and temporary events. These use the values reported in Table 28 but inflated to 2012 prices following the manufacturer's methodology, using a multiplier of 282.5/267.0.[78]
- Assessing the impact if patients withdrawing from a nalmefene-related adverse event also withdrew from PI. Two scenarios were run assuming all patients that had a nalmefene-related adverse event withdrew from PI and assuming that 50% of those with a nalmefene-related adverse event withdrew from PI
- Assuming that 50% of patients received outpatient medically assisted withdrawal and 50% received home-based medically assisted withdrawal. Using the midpoint of the range from NICE CG115 this equated to a cost per medically assisted withdrawal of £645.
- Assuming that the costs of serious and temporary events were zero and that the utility was the same as for those drinking at a very high-risk level. This is not deemed plausible but assesses the impact of these variables on the ICER.
- That the cost of a specialist prescribing face-to-face contact was £119 rather than £94 in accordance with more recent data.

The ERG base case incorporated each of the points above, with the assumption that 50% of those patients who had a nalmefene-related adverse event would also drop-out from PI based on clinical advice provided to the ERG. An additional analysis was undertaken on the ERG base case to examine the impact of not allowing second line treatment options to assess the robustness of the results to this assumption.

Table 42: Exploratory Analyses undertaken by the ERG in Comparison 1

Code	Change from MS base case	Total costs		Total QALYs		Incremental costs	Incremental QALYs	ICER
		NMF + PI	PI alone	NMF + PI	PI alone			
MS base case	-	£4,445	£4,842	3.624	3.553	-£397	0.071	NMF + PI dominates
1	Medium-risk drinkers assumed to relapse to high- / very high-risk	£4,803	£5,240	3.608	3.538	-£437	0.070	NMF + PI dominates
2	Alternative costs for serious and temporary events	£4,721	£5,182	3.624	3.553	-£461	0.071	NMF + PI dominates
3	All patients who withdraw for NMF-related reasons also withdraw from PI	£4,685	£4,842	3.607	3.553	-£157	0.055	NMF + PI dominates
4	Half of patients who withdraw for NMF-related reasons also withdraw from PI	£4,565	£4,842	3.616	3.553	-£277	0.063	NMF + PI dominates
5	Assuming an average cost of medically assisted withdrawal of £645 per patient	£4,186	£4,438	3.624	3.553	-£253	0.071	NMF + PI dominates
6	Costs of specialist prescribing face to face contact set to £119	£4,560	£4,945	3.624	3.553	-£385	0.071	NMF + PI dominates
7	Costs of serious or temporary events set to £0 and associated utility set to that of very high-risk drinkers.	£3,625	£3,811	3.685	3.623	-£186	0.062	NMF + PI dominates
ERG Base Case	1 + 2 + 4 + 5 + 6	£4,925	£5,205	3.601	3.538	-£280	0.063	Nalmefene + PI dominates
ERG Base Case but no second-line treatment options are allowed		£3,270	£2,978	3.528	3.455	£292	0.073	£4,013

NMF: Nalmefene; PI: Psychosocial Intervention

Superseded – see Erratum

Although the ERG was critical of the fact that the manufacturer did not conduct half-cycle correction the model was not adapted by the ERG to allow this. This decision was made for the following reasons: that the time required to amend the model was not insignificant; and that after the first year (in which monthly cycles were used) there was no differential efficacy between the two arms apart from those drinking at medium-risk levels; and that any potential inaccuracy was relatively small compared with the uncertainty within Comparisons 2 and 3.

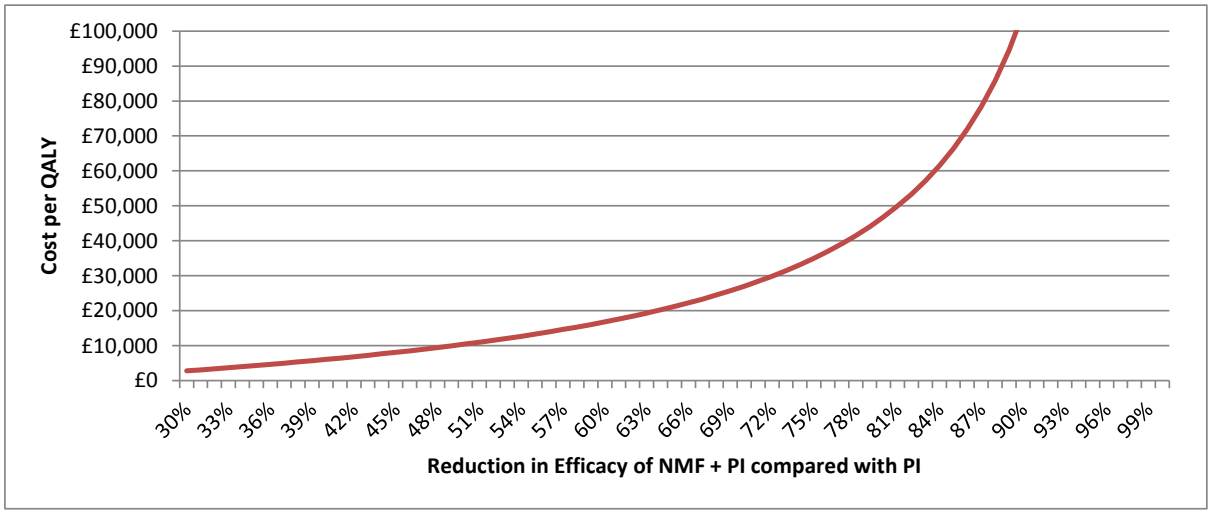
The clinical advisors to the ERG did not agree with the assumption that patients would remain on treatment (regardless of drinking risk level) for the full year. It was believed that GPs would not let patients drink at very-high risk levels for greater than 6 months without recommending intensification of treatment and additional specialist input, and that 3 months might be a more likely cut-off point. This point was discussed within the clarification round (Question A2) with the manufacturer maintaining that the 12 months' duration was appropriate as the patients were initially only mildly dependent with no features of withdrawal. This remains an issue of disagreement, and the manufacturer provides no evidence as to why the patients all meet the criteria for medically assisted withdrawal at 12 months rather than at 6 months or 60 months. This issue will add uncertainty to the cost-effectiveness ratio, although it is not clear whether such changes would be favourable or unfavourable to nalmefene. The ERG comment that it is highly unlikely to change the conclusion that nalmefene in addition to PI is cost-effective in Comparison 1.

5.3.2 The exploratory ERG analyses in Comparison 2

The ERG believes that the assumption that people still at medium-risk drinking levels at 12 months would be unlikely to be treated indefinitely whilst in the medium-risk level and have assumed in Comparison 1 that these patients would relapse to high- and very high-risk levels. However, the model submitted by the manufacturer following the clarification period which included this function did not operate correctly with respect to the 'variable treatment' option which is used to undertake the threshold analyses regarding the reduction in benefit of nalmefene plus PI compared with PI alone (Scenario Analyses 7). Given that the impact on the ICER was small (Table 41) the ERG has assumed that patients will receive treatment continually whilst in the medium-risk drinking level for Comparison 2.

The threshold analyses undertaken by the manufacturer in Scenario Analysis 7 was re-undertaken using the ERG base case (with the exception that those at a medium-risk drinking level were assumed to remain on treatment). The results are shown in Figure 19.

Figure 19: Threshold analysis undertaken by the ERG regarding the efficacy of nalmefene and PI compared with PI alone



The results produced by the ERG are similar to those produced by the manufacturer in that if the efficacy of nalmefene and PI compared with PI alone were reduced by 63.7% then the cost per QALY would become £20,000. The reduction would have to be 72.0% for the cost per QALY to reach £30,000. The ERG comment that the uncertainties in the ICER regarding the lack of half cycle correction and the duration for which patients would be allowed to remain in the high- / very high-risk level also apply to these results. Additionally the threshold values were calculated using deterministic results which may be unfavourable to nalmefene. The clinical advisors to the ERG did not feel confident in expressing an opinion on whether the actual reduction would be greater or lower than a 60-70% threshold.

Superseded – see Erratum

Additional analyses including costs of crime and justice were undertaken, albeit with the caveat that the methodology used may not be valid. In this circumstance the reduction would need to be 80.6% for the cost per QALY of the addition of nalmefene to be £20,000 and be 83.3% for the cost per QALY to be £30,000.

5.3.3 The exploratory ERG analyses in Comparison 3

There are very few appropriate data to assess the cost-effectiveness of nalmefene with PI as recommended in NICE CG115 with PI as recommended in NICE CG115 supplemented with nalmefene in those that did not have a positive response to PI. The evaluation is also made more complex by the time point at which PI alone is assumed to have not been successful is not defined. Data from the pivotal trials indicate that approximately 20% of patients had low-risk drinking levels or were abstinent at month 3 on BRENDA alone. It is expected that a greater response rate would be observed were higher intensity PI as recommended in NICE CG115 used. The ERG believe it

probable that in such people the costs of nalmefene can be saved without incurring health losses, which could be the most cost-effective strategy. Although uncertainty would exist regarding the efficacy of nalmefene in those who had not responded to PI.

Such an argument can also be applied should immediate nalmefene not deemed cost-effective in Comparison 2. Delayed nalmefene use is likely to improve the cost-effectiveness of nalmefene and increase the threshold of reduction in efficacy required for nalmefene to have a cost per QALY of £20,000 or £30,000, although uncertainty would exist regarding the efficacy of nalmefene in those who had not responded to PI.

5.3.4 The exploratory ERG analyses in Comparison 4

There are very few appropriate data to assess the cost-effectiveness of nalmefene (immediately or reserved for those who have not responded to PI) with PI against off-label naltrexone and PI for those who have not responded to PI alone. In all cases PI is as recommended in NICE CG115. As such the ERG does not feel comfortable in providing an estimate of the ICER for this comparison.

5.4 Conclusions of the cost effectiveness section

The ERG believes that the manufacturer has estimated a plausible ICER in Comparison 1 (albeit an analysis that did not meet the decision problem in the final scope). The ERG believes that the threshold for the reduction in efficacy of nalmefene where PI is that recommended in CG115 is slightly favourable to nalmefene in Comparison 2.

The manufacturer did not estimate an ICER for Comparison 3 and comment in the second round of clarification questions that “There are no data available allowing a precise assessment of nalmefene as a second line treatment for patients failing psychosocial intervention.” The ERG concurs with this statement. However, the ERG states that it is probable that delayed use of nalmefene in patients who do not respond to PI as recommended by NICE CG115 is more cost-effective than immediate use of nalmefene in all patients. The delayed use of nalmefene would also be aligned with the recommendation for pharmacotherapy use in NICE CG115, although these were written before the licensing of nalmefene.

The manufacturer did not estimate an ICER for Comparison 4. Neither has the ERG, with the one difference being that the ERG acknowledges that such a comparison should be made were data available. The ERG does not speculate on whether the Appraisal Committee would decide that naltrexone was, or was not, a valid comparator.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

None of the analyses undertaken by the ERG markedly changed the ICER calculated by the manufacturer. As such the estimated ICERs are similar. The one notable difference concerns the discussion of the likely cost-effectiveness of delaying nalmefene and only using it in those patients who do not respond to PI alone within a clinician-defined time period, which is considered within the ERG report but omitted from the MS. Whilst the ERG does not present an ICER for this comparison it believes it probable that delayed treatment reserved for those who do not respond to PI alone is more cost-effective than immediate treatment for all patients. Comparison 4 has been considered in this report, albeit with no ICER estimated, but was omitted from the MS. For summary purposes the results produced by the ERG are reproduced in Table 43.

Table 43: Summary of ERG cost-effectiveness conclusions

Comparison	ERG evaluation
1. A comparison of nalmefene plus PI being compared with PI alone with PI being approximated by BRENDA as used in the pivotal RCTs.	Nalmefene dominates.
2. A comparison of nalmefene plus PI being compared with PI alone with PI being that recommended in NICE CG115.	If the efficacy benefit of nalmefene plus PI shown in the pivotal trials is not reduced by more than 63% if BRENDA was replaced by PI as recommended in NICE CG115 then the cost per QALY of the addition of nalmefene remains below £20,000. If costs related to the crime and justice system are included this threshold value rises to 80%, albeit with the caveats on the validity of the methodology.
3. A comparison of delayed nalmefene use for those who did not respond to PI as recommended in NICE CG115 with immediate use of nalmefene in addition to PI as recommended in NICE CG115.	No data are available to make a robust estimate of the cost-effectiveness although the ERG believes it probable that delayed nalmefene would be a cost-effective strategy.
4. A comparison of delayed (or immediate) nalmefene use for those who did not respond to PI as recommended in NICE CG115 with off-label use of naltrexone in addition to PI for those that did not respond to PI alone as recommended in NICE CG115.	No data are available to make a robust estimate of the cost-effectiveness. The ERG do not feel comfortable providing an ICER for this comparison

7 END OF LIFE CONSIDERATION

NICE end of life supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
- The treatment is licensed or otherwise indicated, for small patient populations.

The manufacturer make no claim that nalmefene should be appraised under the supplementary 'end of life' advice. The ERG would concur with this view.

8 OVERALL CONCLUSIONS

There is considerable agreement between the manufacturer and the ERG regarding the ICERs for Comparison 1 (an evaluation outside of the final scope) and reasonable agreement in the threshold values estimated for Comparison 2. Given the small number of UK patients in the pivotal studies means that the generalisability of results to England and Wales is unclear.

There are no ideal data to populate Comparison 3 although the ERG believes that delayed initiation of nalmefene in those who do not respond to PI as recommended in NICE CG115 is probably more cost-effective than immediate initiation of nalmefene in all patients. The delayed use of nalmefene would also be aligned with the recommendation for pharmacotherapy use in NICE CG115, although these were written before the licensing of nalmefene. There are no ideal data to populate Comparison 4 and the ERG does not feel comfortable providing an ICER for this comparison.

8.1 Implications for research

Key research implications are bulleted below.

- Data are required on the relative efficacy of nalmefene in addition to PI and PI alone where PI conforms to that recommended in NICE CG115.
- Data are required on the relative efficacy of immediately initiating nalmefene in addition to PI for all patients compared with PI alone followed by nalmefene in those patients who do not respond to PI alone. In both cases PI should conform to that recommended in NICE CG115.
- Data are required on the relative efficacy of nalmefene (either used immediately or reserved for those patients who did not respond to PI) compared with off-label naltrexone reserved for those patients who did not respond to PI. In both cases PI should be as recommended in NICE CG115.

9 APENDICES

Appendix 1: Outcomes data for each trial (reproduced: manufacturer's clarification response to question B6 – Appendix 4)

Table 44: Number of heavy drinking days (days/month)

Trial	Trial Arm	Baseline		Adjusted Change From Baseline at Month 6			Difference From Placebo + PI		
		N	Mean ± SD	N	Mean ± SE	95% CI	Mean ± SE	95% CI	p-value
ESENSE 1	Placebo + PI	167	23.1 ± 5.4	114	–8.0 ± 1.0	[–9.8, –6.1]	–3.7 ± 1.0	[–5.9; –1.5]	0.0010
	Nalmefene + PI	171	23.0 ± 5.9	85	–11.6 ± 1.0	[–13.6; –9.6]			
ESENSE 2	Placebo + PI	155	21.6 ± 6.4	111	–10.2 ± 0.9	[–12.1; –8.4]	–2.7 ± 1.2	[–5.0; –0.3]	0.0253
	Nalmefene + PI	148	22.7 ± 6.0	103	–12.9 ± 0.9	[–14.7; –11.0]			
SENSE	Placebo + PI	42	18.6 ± 6.4	29[a]	–8.6 ± 1.4[a]	[–11.3; –5.9] [a]	–3.6 ± 1.5[a]	[–6.5; –0.7][a]	0.0164[a]
	Nalmefene + PI	141	19.1 ± 6.3	78[a]	–12.2 ± 0.9[a]	[–14.0; –10.4][a]			

CI = confidence interval; HDD = heavy drinking day; PI = psychosocial intervention; SD = standard deviation; SE = standard error.

[a] Month 13.

Table 45: Total alcohol consumption (g/day)

Trial	Trial Arm	Baseline		Adjusted Change From Baseline at Month 6			Difference From Placebo + PI		
		N	Mean ± SD	N	Mean ± SE	95% CI	Mean ± SE	95% CI	p-value
ESENSE 1	Placebo + PI	167	98.7 ± 40.5	114	–40.0 ± 3.9	[–47.6; –32.3]	–18.3 ± 4.4	[–26.9; –9.7]	< 0.0001
	Nalmefene + PI	171	102.2 ± 42.9	85	–58.3 ± 4.1	[–66.4; –50.2]			
ESENSE 2	Placebo + PI	155	108.0 ± 47.4	111	–60.1 ± 4.0	[–68.0; –52.3]	–10.3 ± 5.0	[–20.2; –0.5]	0.0404
	Nalmefene + PI	148	113.0 ± 48.0	103	–70.4 ± 4.0	[–78.3; –62.6]			
SENSE	Placebo + PI	42	100.6 ± 46.9	29[a]	–49.7 ± 6.4[a]	[–62.4; –37.1][a]	–17.3 ± 6.8[a]	[–30.9; –3.8][a]	0.0129[a]
	Nalmefene + PI	141	100.4 ± 45.0	78[a]	–67.1 ± 4.3[a]	[–75.5; –58.6][a]			

CI = confidence interval; PI = psychosocial intervention; SD = standard deviation; SE = standard error.

[a] Month 13.

Appendix 2: Pooled (ESENSE1 and ESENSE2 trials) secondary outcome results: Licensed population

Table 46: Responder analyses - Odds ratio for response in the patients with a high/very high DRL at baseline and randomisation: Licensed population (p95, MS and manufacturers clarification response to question B6)

Responder analysis	Trial	Trial Arm	N	% of Responders	Odds ratio for response at month 6	95% CI	p-value
RSDRL (response defined as a downward shift from baseline in DRL by two risk categories							
	ESENSE 1	Placebo + PI	167	42.5	2.15	[1.38; 3.36]	< 0.001
		Nalmefene + PI	171	60.8			
	ESENSE 2	Placebo + PI	155	41.3	1.59	[0.98; 2.59]	0.062
		Nalmefene + PI	148	52.0			
					Pooled estimate[a]		
					1.87	1.35;2.59	< 0.001
RLDRL response defined as a downward shift from baseline in DRL to low DRL or lower							
	ESENSE 1	Placebo + PI	167	29.3	2.12	[1.34; 3.39]	0.001
		Nalmefene + PI	171	45.6			
	ESENSE 2	Placebo + PI	155	34.2	1.44	[0.86; 2.42]	0.170
		Nalmefene + PI	148	40.5			
					Pooled estimate[a]		
					1.79	1.27;2.53	< 0.001
≥ 70% Reduction in total alcohol consumption							
	ESENSE 1	Placebo + PI	167	21.0	2.22	[1.34; 3.72]	0.002
		Nalmefene + PI	171	35.7			
	ESENSE 2	Placebo + PI	155	31.0	1.63	[0.98; 2.71]	0.058
		Nalmefene + PI	148	41.2			
					Pooled estimate[a]		
					1.88	1.32; 2.70	< 0.001

CI, confidence interval; PI, psychosocial intervention

[a] Pooled estimate based on individual patient data: full analysis set using the mixed model repeated measures analysis approach

Table 47: SF-36 component summary score mean change from baseline to month 6 in patients with high/very high drinking risk level at screening and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population (reproduced: p100, MS and manufacturers clarification response to question B6)

Trial	Trial Arm	Baseline		Change From Baseline to Month 6		Difference From Placebo + PI		
		N	Mean ± SD	N	Mean ± SE	Mean ± SE	95% CI	p-value
ESENSE 1	Physical Component Summary							
	Placebo + PI	166	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	167	[redacted]	[redacted]	[redacted]			
	Mental Component Summary							
	Placebo + PI	166	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	167	[redacted]	[redacted]	[redacted]			
ESENSE 2	Physical Component Summary							
	Placebo + PI	148	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	146	[redacted]	[redacted]	[redacted]			
	Mental Component Summary							
	Placebo + PI	148	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	146	[redacted]	[redacted]	[redacted]			

CI, confidence interval; PI, psychosocial intervention; SD, standard deviation; SE, standard error; SF-36, SF-36 Health Survey.

Table 48: SF-36 adjusted mean change from baseline to month 6 in pooled ESENSE1 and ESENSE2 (MMRM, FAS): observed cases–licensed population (reproduced: p101, MS and manufacturers clarification response to question B6)

Score	Change from baseline to month 6			Difference to placebo		
	Intervention	N	Mean ± SE	Mean ± SE	95% CI	p-value
SF-36 mental component score	NMF + PI	184	5.74 ± 0.79	3.09 ± 0.92	1.29-4.89	0.0008
	PBO + PI	218	2.65 ± 0.78			
SF-36 physical component score	NMF + PI	184	2.35 ± 0.48	1.23 ± 0.55	0.15-2.31	0.0259
	PBO + PI	218	1.12 ± 0.47			

CI, confidence interval; FAS, full analysis set; MMRM, mixed model repeated measures; NMF, nalmefene; PBO, placebo; PI, psychosocial intervention; SE, standard error (Note: A lower score indicates fewer alcohol-related problems.)

Table 49: EQ-5D score mean change from baseline to month 6 in patients with high/very high DRL at screening and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population (reproduced: p102, MS and manufacturers clarification response to question B6)

Trial	Trial Arm	Baseline		Change From Baseline to Month 6		Difference From Placebo + PI		
		N	Mean ± SD	N	Mean ± SE	Mean ± SE	95% CI	p-value
ESENSE 1	Health State							
	Placebo + PI	164	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	170	[redacted]	[redacted]	[redacted]			
	Utility Index							
	Placebo + PI	166	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	170	[redacted]	[redacted]	[redacted]			
ESENSE 2	Health State							
	Placebo + PI	151	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	147	[redacted]	[redacted]	[redacted]			
	Utility Index							
	Placebo + PI	152	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nalmefene + PI	147	[redacted]	[redacted]	[redacted]			

CI, confidence interval; EQ-5D, EuroQol 5-dimension; PI, psychosocial intervention; SD, standard deviation; SE, standard error.

Table 50: EQ-5D adjusted mean change from baseline to month 6 in pooled ESENSE1 and ESENSE2 (MMRM, FAS): observed cases–licensed population (reproduced: p103, MS and manufacturers clarification response to question B6)

Score	Change from baseline to month 6			Difference to placebo		
	Intervention	N	Mean ± SE	Mean ± SE	95% CI	p-value
EQ-5D utility index score	NMF + PI	188	0.06 ± 0.01	0.03 ± 0.02	0.00-0.06	0.0445
	PBO + PI	222	0.03 ± 0.01			
EQ-5D health state score	NMF + PI	189	6.60 ± 1.20	3.46 ± 1.38	0.75-6.17	0.0124
	PBO + PI	221	3.13 ± 1.19			

CI, confidence interval; FAS, full analysis set; MMRM, mixed model repeated measures; NMF, nalmefene; PBO, placebo; PI, psychosocial intervention; SE, standard error (Note: A lower score indicates fewer alcohol-related problems.)

Table 51: Drinker Inventory of Consequences total score at Month 6 (reproduced: manufacturer's clarification response to question B6)

Trial	Trial Arm	Baseline		Change From Baseline to Month 6		Difference From Placebo + PI		
		N	Mean	N	Mean ± SE	Mean ± SE	95% CI	p-value
ESENSE 1	Placebo + PI	166	35.0	133	–11.8 ± 1.5	–3.7 ± 1.6	[–6.8; –0.5]	0.022
	Nalmefene + PI	170	35.2	87	–15.5 ± 1.6			
ESENSE 2	Placebo + PI	154	48.8	105	–17.2 ± 1.1	–2.7 ± 2.5	[–7.6; 2.2]	0.284
	Nalmefene + PI	147	48.2	101	–19.9 ± 2.1			

CI, confidence interval; PI, psychosocial intervention; SE, standard error (Note: A lower score indicates fewer alcohol-related problems.)

Table 52: Drinker Inventory of Consequences total score - adjusted mean change from baseline to month 6 in ESENSE1 and ESENSE2 pooled (MMRM, FAS): observed cases–licensed population (reproduced: p103, MS and manufacturers clarification response to question B6)

Score	Change from baseline to month 6			Difference to placebo		
	Intervention	N	Mean ± SE	Mean ± SE	95% CI	p-value
DrInC-2R total score	NMF + PI	189	−17.86 ± 1.31	−3.22 ± 1.47	−6.12 to −0.33	0.0292
	PBO + PI	226	−14.64 ± 1.30			

CI, confidence interval; DrInc-2R, The Drinker Inventory of Consequences–Recent Drinking ' FAS, full analysis set; MMRM, mixed model repeated measures; NMF, nalmefene; PBO, placebo; PI, psychosocial intervention; SE, standard error (Note: A lower score indicates fewer alcohol-related problems.)

Appendix 3: ERG update search on the cost-effectiveness of nalmefene (since 2013) and for the cost-effectiveness search of naltrexone

Medline: Ovid. 1946 to Present
94 records

1 (nalmefene or revex or selincro).tw. (233)
2 Naltrexone/ (6540)
3 (naltrexone or revia or depade or vivitrol or celupan or trexan or nemexin or nalorex or antaxone or en-1639a or en 1639a or en1639a).tw. (5263)
4 2 or 3 (7948)
5 Economics/ (26516)
6 "costs and cost analysis"/ (41432)
7 Cost-benefit analysis/ (59066)
8 Cost control/ (20078)
9 Cost savings/ (8570)
10 Cost of illness/ (17228)
11 Cost sharing/ (1906)
12 "deductibles and coinsurance"/ (1413)
13 Medical savings accounts/ (480)
14 Health care costs/ (26580)
15 Direct service costs/ (1018)
16 Drug costs/ (11992)
17 Employer health costs/ (1061)
18 Hospital costs/ (7630)
19 Health expenditures/ (13513)
20 Capital expenditures/ (1940)
21 Value of life/ (5383)
22 exp economics, hospital/ (19268)
23 exp economics, medical/ (13512)
24 Economics, nursing/ (3889)
25 Economics, pharmaceutical/ (2510)
26 exp "fees and charges"/ (26737)
27 exp budgets/ (11988)
28 (low adj cost).mp. (24436)
29 (high adj cost).mp. (7989)
30 (health?care adj cost$).mp. (4381)
31 (fiscal or funding or financial or finance).tw. (81603)
32 (cost adj estimate$).mp. (1432)
33 (cost adj variable).mp. (32)
34 (unit adj cost$).mp. (1560)
35 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (174485)
36 or/5-35 (466549)
37 1 and 36 (6)
38 4 and 36 (95)
39 36 and 37 (6)

Embase:Ovid. 1974 to 2014 March 26
356 records

1 nalmefene/ (900)
2 (nalmefene or revex or selincro).tw. (330)
3 1 or 2 (912)
4 naltrexone/ (11069)

5 (naltrexone or revia or depade or vivitrol or celupan or trexan or nemexin or nalorex or antaxone or en-1639a or en 1639a or en1639a).tw. (6674)
6 4 or 5 (11701)
7 Socioeconomics/ (107928)
8 Cost benefit analysis/ (63747)
9 Cost effectiveness analysis/ (95938)
10 Cost of illness/ (13903)
11 Cost control/ (47700)
12 Economic aspect/ (102673)
13 Financial management/ (99755)
14 Health care cost/ (126796)
15 Health care financing/ (11360)
16 Health economics/ (33351)
17 Hospital cost/ (13536)
18 (fiscal or financial or finance or funding).tw. (102841)
19 Cost minimization analysis/ (2427)
20 (cost adj estimate$).mp. (1951)
21 (cost adj variable$).mp. (154)
22 (unit adj cost$).mp. (2385)
23 or/7-22 (655372)
24 3 and 23 (29)
25 6 and 23 (356)

NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
8 records

#1 nalmefene or revex or selincro:ti,ab,kw
#2 (naltrexone or revia or depade or vivitrol or celupan or trexan or nemexin or nalorex or antaxone or en-1639a or en 1639a or en1639a):ti,ab,kw

EconLit: Ovid. 1886 to February 2014
0 records

1 (nalmefene or revex or selincro).tw. (0)
2 (naltrexone or revia or depade or vivitrol or celupan or trexan or nemexin or nalorex or antaxone or en-1639a or en 1639a or en1639a).tw. (0)

10 REFERENCES

1. World Health Organization (WHO). The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: WHO; 1992.

2. Drummond, C., Oyefeso, A., Phillips, T., Cheeta, S., Deluca, P., Perryman, K. *et al*. Alcohol needs assessment research project (ANARP). London: Department of Health; 2005.

3. National Collaborating Centre for Mental Health. Alcohol-use Disorders. The NICE Guideline on Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. National Clinical Practice Guideline 115. *NICE* 2011.

4. Fuller, E., Jotangia, D., Farrell, M. Alcohol misuse and dependence. Adult psychiatric morbidity in England, 2007. Results of a household survey. McManus S, Meltzer H, Brugha T, *et al*., editors. Leeds: NHS Information Centre for Health and Social Care; 2009.

5. All Wales Theapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report: Nalmefene (Selincro) 18mg film-coated tablets. Reference number: 1259. 2013.

6. Rehm, J., Scafato, E. Indicators of alcohol consumption and attributable harm for monitoring and surveillance in European Union countries. *Addiction* 2014; 106:4-10.

7. Rehm, J., Shield, K., Rehm, M., Gmel, G., Frick, U. Alcohol consumption, alcohol dependence and attributable burden of disease in Europe: potential gains from effective interventions for alcohol dependence. Canada: Centre for Addiction and Mental Health (CAMH); 2012.

8. English, D., Holman, C., Milne, E., Winter, M., Hulse, G., Codde, J. *et al*. The quantification of drug caused morbidity and mortality in Australia. Canberra, Australia: Commonwealth Department of Human Services and Health; 1995.

9. Rehm, J., Roerecke, M. Reduction of drinking in problem drinkers and all-cause mortality. *Alcohol and Alcoholism* 2013; 48(4):509-513.

10. Alcohol Concern. Key statistics and facts. Available at: http://ac.demo.me.uk/consultancy-and-training/resources2/resources/key-stats-and-facts. Accessed 2 April 2014.

11. Starosta, A., Leeman, R., Volpicelli, J. The BRENDA model: integrating psychosocial treatment and pharmacotherapy for the treatment of alcohol use disorders. *J Psychiatr Pract* 2006; 12(2):80-89.

12. National Institute for Health and Care Excellence (NICE). Alcohol-use disorders: preventing harmful drinking (PH 24). 2010.

13. Moyer, A., Finney, J., Swearingen, C., Vergun, P. Brief interventions for alcohol problems: a meta-analytic review of controlled investigations in treatmentseeking and non-treatment-seeking populations. *Addiction* 2002; 97:279-292.

14. Lundbeck Limited. Nalmefene (Selincro) - ssummary of product characteristics. Denmark: H. Lundbeck A/S; 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002583/WC500140255.pdf Accessed 1 April 2014.

15. European Medicines Agency (EMA). Selincro (nalmefene) assessment report. 13 December 2012. EMA/78844/2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002583/WC500140326.pdf Accessed 1 April 2014.

16. Joint Formulary Committee. March ed. *British National Formulary*. London: BMJ Group and Pharmaceutical Press; 2014.

17. European Medicines Agency (EMA). Guideline on the development of medicinal products for the treatment of alcohol dependence. EMA; 2010. Available at: http://www.emea.europa.eu/docs/en_GB/ document_library/Scientific_guideline/2010/03/WC500074898.pdf. Accessed 2 April 2014.

18. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. NICE; 2013.

19. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.

20. Centre for Reviews and Dissemination. Systematic review: CRD's guidance for undertaking reviews in health care. York: University of York; 2009.

21. Dundar, Y., Dodd, S., Williamson, P., Dickson, R., Walley, T. Case study of the comparison of data from conference abstracts and full-text articles in health technology assessment of rapidly evolving technologies: does it make a difference? *Int J Technol Assess Health Care* 2006; 22:288-294.

22. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal (STA) - Specification for manufacturer/sponsor submission of evidence. London: NICE; 2012.

23. Egger, M., Smith, G., Phillips, A. Meta-analysis: principles and procedures. *British Medical Journal* 1997; 315:1533-1537.

24. Lievre, M., Cucherat, M., Leizorovicz, A. Pooling, meta-analysis, and the evaluation of drug safety. *Current Controlled Trials in Cardiovascular Medicine* 2002; 3(1):6.

25. Bravata, D., Olkin, I. Simple pooling versus combining in meta-analysis. *Eval Health Prof* 2009; 24:218-230.

26. Anton, R., Pettinati, H., Zweben, A., Kranzler, H., Johnson, B., *et al*. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. *J Clin Psychopharmacol* 2004; 24(4):421-428.

27. Karhuvaara, S., Simojoki, K., Virta, A., Rosberg, M., Loyttyniemi, E., *et al*. Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. *Alcohol Clin Exp Res* 2007; 31(7):1179-1187.

28. Mann, K., Bladstrom, A., Torup, L., Gual, A., van den Brink, W. Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. *Biol Psychiatry* 2013; 73(8):706-713.

29. van den Brink, W., Aubin, H.J., Bladstrom, A., Torup, L., Gual, A., Mann, K. Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level:

results from a subgroup analysis of two randomized controlled 6-month studies. *Alcohol Alcohol* 2013; 48(5):570-578.

30. Lundbeck. Clinical study report 12014A. *Lundbeck* 2012.

31. Gual, A., He, Y., Torup, L., van den Brink, W., Mann, K. ESENSE2 Study Group. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. *Eur Neuropsychopharmacol* 2013; 23(11):1432-1442.

32. Lundbeck. Clinical study report 12013A. *Lundbeck* 2012.

33. van den Brink W, Sorensen P, Torup L, Gual A. Long-term efficacy, tolerability, and safety of nalmefene as-needed in alcohol-dependence: A randomised, double-blind, placebo-controlled study. Presented at the 35th Annual Scientific Meeting of the Research Society on Alcoholism; 23-27 June 2012. San Francisco, CA. Alcohol ClinExp Res. 36, 247A.

34. van den Brink, W., Sorensen, P., Torup, L., Mann, K., Gual, A., for the SENSE Study Group. Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. *J Psychopharmacol* 2014; [Epub ahead of print] PubMed PMID: 2467134.

35. Babor, T., Steinber, K., Anton, R., *et al*. Talk is cheap: Measuring drinking outcomes in clinical trials. *J Stud Alcohol* 2000; 6(1):55-63.

36. Maisto, S., Sobell, M., Mitch Cooper, A., Sobell, L. Test-Retest reliability of retrospective self-reports in three populations of alcohol abusers. *J Behav Assessment* 1979; 1(4):315-326.

37. Maisto, S., Conigliaro, J., Gordon, A., McGinnis, K., Justice, A. An experimental study of the agreement of self-administration and telephone administration of the Timeline Followback interview. *J Stud Alcohol Drugs* 2008; 69(3):468-471.

38. Sobell LC, Sobell MB. Alcohol timeline followback (TLFB). In: Rush AJ, First MB, Blacker D, editors. Handbook of psychiatric measures. Arlington, VA: American Psychiatric Publishing Inc.; 2008

39. Dumville, J., Torgerson, D., Hewitt, E. Reporting attrition in randomised controlled trials. *BMJ* 2006; 332:969-971.

40. Fergusson, D., Aaron, S., Guyatt, G., Hebert, P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002; 325:652-654.

41. Hollis, S., Campbell, F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 2014; 319:670-674.

42. Heinala, P., Alho, H., Kiianmaa, K., Lonnqvist, J., Kuoppasalmi, K., Sinclair, J.D. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2001; 21(3):287-292.

43. Kranzler, H., Armeli, S., Tennen, H., Blomqvist, O., Oncken, C., Petry, N. *et al*. Targeted naltrexone for early problem drinkers. *J Clin Psychopharmacol* 2003; 23(3):294-304.

44. Hernandez-Avila, C., Song, C., Kuo, L., Tennen, H., Armeli, S., Kranzler, H. Targeted versus daily naltrexone: secondary analysis of effects on average daily drinking. *Alcohol Clin Exp Res* 2006; 30(5):860-865.

45. Kranzler, H., Tennen, H., Armeli, S., Chan, G., Covault, J., Arias, A. *et al*. Targeted naltrexone for problem drinkers. *J Clin Psychopharmacol* 2009; 29(4):350-357.

46. Naltrexone [summary of product characteristics]. Middlesex, UK, Accord Healthcare Limited; 2010. Available at: http://www.medicines.org.uk/EMC/medicine/25878/SPC/Naltrexone+Hydrochloride+50+mg+Film-coated+Tablets. Accessed 2 April 2014.

47. Adepend [summary of product characteristics]. Purkersdorf, Austria: Orpha-Devel Handels und Vertriebs GmbH; 2013. Available at: http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1366696837142.pdf. Accessed 2 April 2014.

48. Hester, R., Squires, D., Delaney, H. The Drinker's Check-up: 12-month outcomes of a controlled clinical trial of a stand-alone software program for problem drinkers. *J Subst Abuse Treat* 2005; 28(2):159-169.

49. Alden, L. Behavioral self-management controlled-drinking strategies in a context of secondary prevention. *J Consult Clin Psychol* 1988; 56(2):280-286.

50. Litt, M., Kadden, R., Kabela-Cormier, E., Petry, N. Changing network support for drinking: network support project 2-year follow-up. *J Consult Clin Psychol* 2009; 77(2):229-242.

51. Morgenstern, J., Irwin, T., Wainberg, M., Parsons, J., Muench, F., Bux, D.J. *et al*. A randomized controlled trial of goal choice interventions for alcohol use disorders among men who have sex with men. *J Consult Clin Psychol* 2007; 75(1):72-84.

52. Sandahl, C., Herlitz, K., Ahlin, G., Ronnberg, S. Time-limited group psychotherapy for moderately alcohol dependent patients: a randomized controlled clinical trial. *Psychother Res* 1998; 8:361-378.

53. Vedel, E., Emmelkamp, P., Schippers, G. Individual cognitive-behavioral therapy and behavioral couples therapy in alcohol use disorder: a comparative evaluation in community-based addiction treatment centers. *Psychother Psychosom* 2008; 77(5):280-288.

54. Walitzer, K., Dermen, K., Barrick, C. Facilitating involvement in Alcoholics Anonymous during out-patient treatment: a randomized clinical trial. *Addiction* 2009; 104(3):391-401.

55. Davidson, D., Gulliver, S.B., Longabaugh, R., Wirtz, P.W., Swift, R. Building better cognitive-behavioral therapy: Is broad-spectrum treatment more effective than motivational-enhancement therapy for alcohol-dependent patients treated with naltrexone? *Journal of Studies on Alcohol and Drugs* 2007; 68(2):238-247.

56. Rosenblum, A., Magura, S., Kayman, D., Fong, C. Motivationally enhanced group counseling for substance users in a soup kitchen: a randomized clinical trial. *Drug Alcohol Depend* 2005; 80(1):91-103.

57. Shakeshaft, A., Bowman, J., Burrows, S., Doran, C., Sanson-Fisher, R. Community-based alcohol counselling: a randomized clinical trial. *Addiction* 2002; 97(11):1449-1463.

58. Sobell, L., Sobell, M., Leo, G., Agrawal, S., Johnson-Young, L., Cunningham, J. Promoting self-change with alcohol abusers: a community-level mail intervention based on natural recovery studies. *Alcohol Clin Exp Res* 2002; 26(6):936-948.

59. Marques, A., Formigoni, M. Comparison of individual and group cognitive-behavioral therapy for alcohol and/or drug-dependent patients. *Addiction* 2001; 96(6):835-846.

60. Monti, P., Abrams, D., Binkoff, J., Zwick, W., Liepman, M., Nirenberg, T. *et al*. Communication skills training, communication skills training with family and cognitive behavioral mood management training for alcoholics. *J Stud Alcohol* 1990; 51(3):263-270.

61. Monti, P., Rohsenow, D., Rubonis, A., Niaura, R., Sirota, A., Colby, S. *et al*. Cue exposure with coping skills treatment for male alcoholics: a preliminary investigation. *J Consult Clin Psychol* 1993; 61(6):1011-1019.

62. Sobell, L., Sobell, M. Randomized controlled trial of a cognitive-behavioural motivational intervention in a group versus individual format for substance use disorders. *Psychol Addict Behav* 2009; 23(4):672-683.

63. Kavanagh, D., Sitharthan, G., Young, R., Sitharthan, T., Saunders, J., Shockley, N. *et al*. Addition of cue exposure to cognitive-behaviour therapy for alcohol misuse: a randomized trial with dysphoric drinkers. *Addiction* 2006; 101(8):1106-1116.

64. Walitzer, K., Dermen, K. Alcohol-focused spouse involvement and behavioral couples therapy: evaluation of enhancements to drinking reduction treatment for male problem drinkers. *J Consult Clin Psychol* 2004; 72(6):944-955.

65. Leigh, G., Hodgins, D., Milne, R., Gerrish, R. Volunteer assistance in the treatment of chronic alcoholism. *Am J Drug Alcohol Abuse* 1999; 25(3):543-559.

66. Brookes, S., Whitley, E., Peters, T., Mulheran, P., Egger, M., Davey Smith, G. Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. *Health Technol Assess* 2001; 5(33):1-56.

67. Sun, X., Briel, M., Busse, J., You, J., Aki, E., Mejza, F. et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. *BMJ* 2012; 344:e1553.

68. National Institute for Health and Care Excellence (NICE). ESNM29: Alcohol dependence: nalmefene. NICE; 2013.

69. Walters, D., Connor, J.P., Feeney, G.F., Young, R.M. The cost effectiveness of naltrexone added to cognitive-behavioral therapy in the treatment of alcohol dependence. *Journal of Addictive Diseases* 2009; 28(2):137-144.

70. National Institute for Health and Care Excellence (NICE). Nalmefene for reducing alcohol consumption in people with alcohol dependence. Final scope. *NICE* 2014.

71. Sonnenberg, F., Beck, J. Markov Models in Medical Decision Making: A Practical Guide. Med Decis Making 1993; 13(4):322-338.

72. Naimark, D., Kabboul, N., Krahn, M. The half-cycle correction revisited: redemption of a kludge. Med Decis Making 2013; 33(7):961-970.

73. World Health Organization (WHO). International guide for monitoring alcohol consumption and related harm. WHO/MSD/MSB/00.4. 2000. Available at: http://whqlibdoc.who.int/hq/2000/WHO_MSD_MSB_00.4.pdf. Accessed 21 April 2014.

74. Anderson, P. & Baumberg, B. Alcohol in Europe. London: Institute of Alcohol Studies; 2006. Available at: http://ec.europa.eu/health/archive/ph_determinants/ life_style/alcohol/documents/alcohol_europe_en.pdf. Accessed 21 April 2014.

75. The University of Sheffield. Modelling to assess the effectiveness and cost-effectiveness of public health related strategies and interventions to reduce alcohol attributable harm in England using the Sheffield Alcohol Policy Model, version 2.0. NICE; 2009. Available from http://www.nice.org.uk/nicemedia/live/11828/45668/45668.pdf Accessed 22 April 2014.

76. Taylor, C., Brown, D., Duckitt, A., Edwards, G., Oppenheimer, E., *et al*. Patterns of outcome: drinking histories over ten years among a group of alcoholics. *Br J Addict* 1985; 80(1):45-50.

77. Personal Social Services Research Unit (PSSRU). Unit costs of health & social care 2012. PSSRU; 2012.

78. Personal Social Services Research Unit (PSSRU). Unit costs of health & social care 2013. PSSRU; 2013.

79. The University of Sheffield. Modelling to assess the effectiveness and cost-effectiveness of public health related strategies and interventions to reduce alcohol attributable harm in England using the Sheffield Alcohol Policy Model, version 2.0. University of Sheffield; 2009. Available from http://www.shef.ac.uk/polopoly_fs/1.107991!/file/Appendices.pdf Accessed 22 April 2014.

80. Rittenhouse, B. Potential inconsistencies between cost-effectiveness and cost-utility analyses. An upstairs/downstairs socioeconomic distinction. *Int J Technol Assess Health Care* 1995; 11(2):365-376.

81. Wallace P, Coste F, Chalem Y, François C. Naturalistic disease management study of patients with alcohol dependence in primary care settings in the UK (STREAM). Poster presented at ISPOR annual European conference, Dublin, 2013. Available at: http://www.valueinhealthjournal.com/article/S1098-3015(13)03331-7/abstract Accessed 22 April 2014.