NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Nalmefene for the reduction of alcohol consumption in people with alcohol dependence [ID660]

Manufacturer submission of evidence by Lundbeck Limited

Contents

Executive summary 17
Section A – Decision problem 25
1 Description of technology under assessment 25
2 Context 38
3 Equality 53
4 Innovation 53
5 Statement of the decision problem 57
Section B – Clinical and cost effectiveness 60
6 Clinical evidence 60
7 Cost effectiveness 153
Section C – Implementation 257
8 Assessment of factors relevant to the NHS and other parties 257
9 References 262
10 Appendices 277
11 Related procedures for evidence submission ..... **Error! Bookmark not defined.**

List of tables and figures

Table 1. Base-case cost-effectiveness results 23

Table A1. List of completed trials of nalmefene in adults with alcohol dependence (DSM-IV-TR criteria) 30
Table A2. Unit costs of technology being appraised 33
Table A3. Guidance on alcohol-use disorder issued by NICE and the subgroups addressed 42
Table A4. Percentage of crime attributable to alcohol consumption in England and Wales 56
Table A5. Decision problem 57

Table B1. Eligibility criteria used in the search strategy, level 1 screening for selection of nalmefene and naltrexone studies ... 62
Table B2. Eligibility criteria used in the search strategy, level 2 screening for selection of nalmefene studies 63
Table B3. List of relevant RCTs 66
Table B4. Comparative summary of methodology of ESENSE1, ESENSE2, and SENSE 70
Table B5. Eligibility criteria in the ESENSE1, ESENSE2, and SENSE trials 72
Table B6. Baseline characteristics of patients with a high/very high DRL at baseline and randomisation in ESENSE1 and ESENSE2 (APRS)—licensed population 73
Table B7. Baseline characteristics of patients with a high/very high DRL at baseline and randomisation in the SENSE trial (APRS)—licensed population 75
Table B8. Primary and secondary outcomes of ESENSE1, ESENSE2, and SENSE 78

Table B9. Summary of statistical analyses in ESENSE1, ESENSE2, and SENSE 83
Table B10. Quality assessment results for RCTs 91
Table B11. Mean difference to placebo in the change from baseline to month 6 in HDDs and TAC (FAS; MMRM) in patients with a high/very high DRL at baseline and randomisation (ESENSE1 and ESENSE2): licensed population 93
Table B12. Odds ratio for response secondary efficacy endpoints in the patients with a high/very high DRL at baseline and randomisation (FAS, MMRM): licensed population 95
Table B13. Odds ratio for responder analysis in patients with a high/very high DRL at baseline and randomisation (FAS, MMRM) (pooled data from ESENSE1 and ESENSE2): licensed population 95
Table B14. Changes from baseline to month 6 in CGI-S and CGI-I in patients with a high/very high DRL at baseline and randomisation (FAS, MMRM) (ESENSE1 and ESENSE2): licensed population 97
Table B15. GGT mean change compared with placebo at month 6 in patients with high/very high DRL at screening and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population 98
Table B16. ALAT mean change compared with placebo at month 6 in patients with high/very high DRL at screening and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population 99
Table B17. SF-36 component summary 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 100
Table B18. SF-36 adjusted mean change from baseline to month 6 in pooled ESENSE1 and ESENSE2 (MMRM, FAS): observed cases–licensed population 101
Table B19. 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 102
Table B20. EQ-5D adjusted mean change from baseline to month 6 in pooled ESENSE1 and ESENSE2 (MMRM, FAS): observed cases–licensed population 103
Table B21. DrInC-2R adjusted mean change from baseline to month 6 in ESENSE1 and ESENSE2 pooled (MMRM, FAS): observed cases–licensed population 103
Table B22. Mean difference to placebo in the change from baseline to month 6 or month 13 in HDDs and TAC (FAS, MMRM) in patients with a high/very high DRL at baseline and randomisation (SENSE): licensed population 104
Table B23. Level 2 eligibility criteria used in the search strategy for the selection of studies assessing naltrexone 108
Table B24. Level 1 eligibility criteria used in the search strategy 110

Table B25. Level 2 eligibility criteria used in the search strategy.....111
Table B26. Overview of identified naltrexone studies 114
Table B27. Summary of identified naltrexone trials: study design and outcomes.....115
Table B28. Summary of identified psychosocial interventions trials: study design and outcomes 121
Table B29. Summary of identified naltrexone trials: limitations and feasibility assessment for indirect comparison with nalmefene.....124
Table B30. Summary of results on absolute reduction in drinking reported in the psychosocial intervention trials.....126
Table B31. Treatment-emergent AEs with an incidence of ≥ 5% in either treatment group: total population.....130
Table B32. Treatment-emergent AEs with an incidence of ≥ 5% in either treatment group in patients with a high/very high DRL at baseline and randomisation: licensed population 131
Table B33. Duration of frequent AEs: total population 131
Table B34. Duration of frequent AEs in high/very high DRL at baseline and randomisation: licensed population 132
Table B35. AEs with an incidence of ≥ 0.5% in either treatment group leading to withdrawal: total population.....133
Table B36. AEs with an incidence of ≥ 0.5% in the nalmefene treatment group leading to withdrawal in patients with high/very high DRL at baseline and randomisation: licensed population.....134
Table B37. SAEs in > 1 patient in either treatment group: total population.....135
Table B38. SAEs in > 1 patient in either treatment group in patients with high/very high DRL at baseline and randomisation: licensed population.....136
Table B39. Adherence to medication in the total population and among patients with high/very high DRL at baseline and randomisation (pooled data from ESENSE1, ESENSE2, and SENSE) 138
Table B40. IMP intake of the licensed population (high or very high DRL) (APTS).....139
Table B41. Nalmefene dose intake per drinking level in pooled ESENSE1, ESENSE2, and SENSE pooled: licensed population.....139
Table B42. Number of events per 100,000 patient-years by category of number of HDDs (males and females) 148
Table B43. Number of events per 100,000 patient-years by TAC category (males and females) 149
Table B44. Categorical levels for average volume of pure alcohol per day for women and men 155
Table B45. Patient population in ESENSE1, ESENSE2, and SENSE trials (high and very high WHO DRL at screening and randomisation).....156

Table B46. Main treatment period: adjusted change from baseline I to month 6 in monthly HDDs & TAC (FAS, OC, MMRM) – Study 12014A, 12023A & 12013A - high/very high DRL at baseline & randomisation 156
Table B47. Responder analysis of a downward shift in RSDRL at month 6 (LREG, FAS, OC) – pooled population ESENSE1, ESENSE2 and SENSE 157
Table B48. Alcohol-attributable harmful events 163
Table B49. Alcohol-attributable harmful events 164
Table B50. Key features of analysis 168
Table B51. Transition probabilities from the medium-risk drinking level, years 2 through 5 175
Table B52. General population: annual probability of event 178
Table B53. Drinking per DRL, Year 1 180
Table B54. Drinking per DRL, Years 2 through 5 180
Table B55. Summary of variables applied in the economic model 185
Table B56. Utility values, used to calculate the area under the curve 212
Table B57. Utility values from ESENSE1, ESENSE2, and SENSE, by drinking level used in the base-case analysis 212
Table B58. Utility values for alcohol-attributable serious events 213
Table B59. Utility values for alcohol-attributable short-term events 213
Table B60. Utility values from STREAM, by drinking level used in a sensitivity scenario 214
Table B61. Unit costs associated with nalmefene in the economic model (2012) 220
Table B62. Unit costs associated with secondary abstinence treatment (2011) 222
Table B63. List of alcohol-attributable harmful event costs (2012) 222
Table B64. Crimes included in the model 224
Table B65. Unit cost of crime (2012) 225
Table B66. Scenario analyses performed in the economic analysis of nalmefene cost-effectiveness 227
Table B67. Parameters varied in the one-way sensitivity analysis using a range of interest 229
Table B68. Inputs and associated distributions used in the probabilistic sensitivity analysis 230
Table B69. Number of patients experiencing harmful events at year 5 per 100,000 patients 233
Table B70. Proportion of patients per health state in the model – nalmefene + PI 235
Table B71. Proportion of patients per health state in the model – PI 235
Table B72. QALYs accrued over time: nalmefene + PI 236
Table B73. QALYs accrued over time: nalmefene + PI 236
Table B74. Model outputs by clinical outcomes: nalmefene + PI 236
Table B75. Model outputs by clinical outcomes: PI 237
Table B76. Summary of QALY gain by health state 237
Table B77. Summary of costs by health state (2012) 237
Table B78. Summary of predicted resource use by category of cost (2012) 238
Table B79. Base-case results[a] 239

Table B80. Individual parameters most affecting the cost-effectiveness base-case results in the one-way sensitivity analysis.....240
Table B81. Summary of results of scenario analyses performed in the economic analysis of nalmefene vs. psychosocial support.....243
Table B82. Main findings from the scenario analyses performed in the economic analysis of nalmefene cost-effectiveness.....245
Table B83. Evolution of the proportion of patients per WHO drinking level in the model[a] 248
Table B84. Patient numbers and percentages for England 259
Table B85. Annual budget impact.....261

[Rest of page left intentionally blank]

[Page left intentionally blank]

[Part page left intentionally blank]

Figure A1. Schematic overview of the patient populations in ESENSE1, ESENSE2, and SENSE 27
Figure A2. Relative risk for all-cause mortality by average daily intake of alcohol 39
Figure A3. Reduction of alcohol intake in heavy drinkers and associated mortality risk reduction 40
Figure A4. Schematic of current clinical practice for the management of alcohol dependence in England and Wales 45
Figure A5. Schematic of proposed positioning for nalmefene within clinical practice in England and Wales 46
Figure A6. Increasing risk of at least one negative social consequence by yearly alcohol consumption for selected European countries 55

Figure B1. Flow diagram of identification process for systematic review of nalmefene studies 65
Figure B2. Schematic overview of the study design of ESENSE1 and ESENSE2 68
Figure B3. Schematic overview of the study design of SENSE 69
Figure B4. Patient flow chart in ESENSE1 (study 12014A): licensed population 88
Figure B5. Patient flow chart in ESENSE2 (study 12023A): licensed population 89
Figure B6. Patient flow chart in SENSE (study 12013): licensed population 90
Figure B7. Change from baseline in the number of HDDs among patients with a high/very high DRL at baseline and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population 93

Figure B8. Change from baseline in TAC among patients with a high/very high DRL at baseline and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population 94
Figure B9. Responder analyses at 6 months for patients with high/very high DRL at baseline and randomisation (pooled data from ESENSE1 and ESENSE2): licensed population 96
Figure B10. Change from baseline in CGI-S in patients with a high/very high DRL at baseline and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population 97
Figure B11. Change from baseline in CGI-I in patients with a high/very high DRL at baseline and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population 98
Figure B12. Change from baseline to month 13 in the number of HDDs and TAC observed among patients with a high/very high DRL in SENSE (FAS, MMRM): licensed population 105
Figure B13. Flow diagram of identification process for systematic review (naltrexone) 112
Figure B14. Flow diagram of identification process for systematic review (psychosocial interventions) 113
Figure B15. Sensitivity analyses: change from baseline to month 6 in HDDs (FAS) in patients with a high/very high DRL at baseline and randomisation (ESENSE1 and ESENSE2) 141
Figure B16. Sensitivity analyses: changes from baseline to month 6 in TAC (FAS) in patients with a high/very high DRL at baseline and randomisation (ESENSE1 and ESENSE2) 141
Figure B17. Relationship between alcohol consumption and risk of death due to injuries 150
Figure B18. PRISMA diagram for systematic review of cost-effectiveness studies 154
Figure B19. Summary of the health states incorporated in the model 159
Figure B20. Secondary treatment sequence: alcohol withdrawal followed by acamprosate or oral naltrexone + PI 162
Figure B21. Drop-out sequence 166
Figure B22. Sequence of outcomes in the economic analysis for nalmefene 206
Figure B23. Curves of mean utility scores for nalmefene and placebo over 1 year (ESENSE1, ESENSE2, and SENSE trials) 208
Figure B24. Change from baseline to month 13 in the number of HDDs and TAC observed among patients with a high/very high DRL in SENSE (FAS, MMRM): licensed population 232
Figure B25. Proportion of patients, per WHO DRL, for PI, year 1 232
Figure B26. Proportion of Patients, per WHO DRL, for nalmefene + PI, year 1 233
Figure B27. Results of the base-case analysis, cost-effectiveness scatter plot 241
Figure B28. Results of the base-case analysis, cost-effectiveness acceptability curve 242
Figure B29. Results from scenario 7: threshold effectiveness of PI 244
Figure B30. Proportion of patients, per WHO DRL, for PI, Year 1 248

Figure B31. Proportion of Patients, per WHO DRL, for nalmefene + PI, Year 1 249

Figure 10-2. Patient flow chart in ESENSE1 (study 12014A): total population ..... **Error! Bookmark not defined.**
Figure 10-3. Patient flow chart in ESENSE2 (study 12023A): total population ..... **Error! Bookmark not defined.**
Figure 10-4. Patient flow chart in SENSE (study 12013A): total population **Error! Bookmark no**

Abbreviations

AA	Alcoholics Anonymous
ABPI	Association of the British Pharmaceutical Industry
ACD	Appraisal Consultation Document
AD	alcohol dependence
ADS	Alcohol Dependence Scale
AE	adverse event
ALAT	alanine transaminase
ANCOVA	analysis of covariance
APA	American Psychiatric Association
APQ	Alcohol Problems Questionnaire
APRS	all-patients-randomised set
APSAD	Australasian Professional Society on Alcohol and Other Drugs
APTS	all-patients-treated set
ASAT	aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
AWMSG	All Wales Medicines Strategy Group
BI	brief interventions
BMI	behavioural motivational intervention
BMRCQ	Brief Measure of Readiness to Change Questionnaire
BNF	British National Formulary
BOCF	baseline observation carried forward
CBM	cognitive bias modification
CBT	cognitive behavioural therapy
CDT	carbohydrate-deficient transferrin
CG	Clinical Guideline
CGI-I	Clinical Global Impression-Global Improvement
CGI-S	Clinical Global Impression-Severity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIWA-Ar	Clinical Institute Withdrawal Assessment for Alcohol
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
CS	coping skills
CST	coping skills therapy
DIR	directive approach
DrInC-2R	Drinker Inventory of Consequences
DRL	drinking risk level
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision
ECG	Electrocardiogram

EED	Economic Evaluation Database
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group
FAD	final appraisal determination
FAS	full analysis set
GGT	gamma-glutamyl transpeptidase
GP	general practitioner
GSC	guided self-change
HDD	heavy drinking day
HODaR	Health Outcomes Data Repository
HRG	Healthcare Resource Group
HRQL	health-related quality of life
IAS	Institute of Alcohol Studies
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Version
ICER	incremental cost-effectiveness ratio
IFU	information for use
IMP	investigational medicinal product
INEBRIA	International Network on Brief Interventions for Alcohol
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISRCTN	International Standard Randomised Controlled Trial Number
LDQ	Leeds Dependence Questionnaire
LOCF	last observation carried forward
LREG	logistic regression model
LY	life-year
LYG	life-years gained
MCV	mean corpuscular volume
MeSH	Medical Subject Heading
MET	motivational enhancement therapy
MI	motivational intervention multiple imputation
mITT	modified intention to treat
MMRM	mixed model repeated measures
MOT	motivational enhancement approach
MTP	main treatment period
N/A	not applicable
NCT	National Clinical Trial
NDD	nondrinking days
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMF	Nalmefene
NNTB	number needed to treat to benefit

OC	observed cases
ONS	Office for National Statistics
OR	odds ratio
PBO	Placebo
PbR	payment by results
PH	public health guidance
PI	psychosocial intervention
PICOS	population/patients, intervention, comparison, outcomes, study design
PMI	placebo mean imputation
POMS	Profile of Mood States
PRAC	Pharmacovigilance Risk Assessment Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	personal social services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QS	quality standard
QUOROM	Quality of Reporting of Meta-analyses
R70	≥ 70% reduction in total alcohol consumption
RCT	randomised controlled trial
RLDRL	response defined as a downward shift from baseline in DRL to low DRL or lower
ROP	run-out period
RR	relative risk
RSDRL	response defined as a downward shift from baseline in drinking risk level by two risk categories
RUMQ-ADP	Resource Use Measurement Questionnaire – Alcohol Dependence
SADQ	Severity of Alcohol Dependence Questionnaire
SAE	serious adverse event
SAG	Scientific Advisory Group
SBT	supportive behavioural therapy
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SER	Social and Epidemiological Research
SIGN	Scottish Intercollegiate Guideline Network
SMC	Scottish Medicines Consortium
SPC	summary of product characteristics
STA	single technology appraisal
TAC	total alcohol consumption
TAU	treatment as usual
TLFB	timeline follow-back
UK	United Kingdom
UKATT	UK Alcohol Treatment Trial

US	United States
VAS	visual analogue scale
VASQoL	Visual Analogue Scale Quality of Life
WHO	World Health Organization
WHO-QOL-26	World Health Organization Quality of Life 26-item questionnaire
WTP	willingness to pay

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it has not done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (Sections 10.1 to 10.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked "N/A" and a reason given for this response. The specification should be completed with reference to the NICE document "Guide to the methods of technology appraisal" (www.nice.org.uk), particularly with regard to the "reference case." Users should see NICE's "Guide to the single technology appraisal (STA) process" (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with "see appendix X." Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, "Trial 123/Jones et al.[126]" rather than "One trial[126]").

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see "Related procedures for evidence submission," Section 11.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission.

Registration status, licence and indication

On 28 February 2013, nalmefene (Selincro) was granted a European marketing authorisation for the following indication:

> "The reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (DRL), without physical withdrawal symptoms, and who do not require immediate detoxification. Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Nalmefene should be initiated only in patients who continue to have a high DRL 2 weeks after initial assessment" (Nalmefene summary of product characteristics [SPC], 2013).

For the purposes of the licence, a high DRL is defined by the World Health Organization (WHO) as alcohol consumption ≥ 60 g/day for men and ≥ 40 g/day for women (WHO, 2000).

Consequently, nalmefene is approved for a specific group of alcohol-dependent patients who do *not* require immediate detoxification, who have no physical withdrawal symptoms, for whom a treatment goal of reduction in consumption is appropriate, and who are motivated to change. These patients are equivalent to the NICE Clinical Guideline (CG) 115 definition of "mild" alcohol dependence (NICE, 2011a).

Formulation, dosing, and mechanism of action

Nalmefene is formulated as a film-coated tablet containing 18.06 mg of active ingredient (nalmefene [as hydrochloride dihydrate]). Nalmefene is available in 14- or 28-tablet packs; the acquisition costs are £42.42 and £84.84, respectively (British National Formulary [BNF], 2013).

Nalmefene is an opioid receptor modulator with a distinct μ, δ, and κ receptor profile. Nonclinical and clinical research suggests that alcohol intake has reinforcing properties that are, at least in part, mediated through the endogenous opioid system. In vitro studies have demonstrated that nalmefene is a selective opioid receptor ligand with antagonist activity at the μ and δ receptors and partial agonist activity at the κ receptor. In vivo studies suggest that nalmefene acts at the cortico-mesolimbic circuit to help reduce alcohol consumption.

Nalmefene is to be taken "as needed": on each day the patient perceives a risk of drinking alcohol, 1 tablet should be taken, preferably 1 to 2 hours prior

to the anticipated time of drinking. If the patient has started drinking alcohol without taking nalmefene, the patient should take 1 tablet as soon as possible. The maximum dose of nalmefene is 1 tablet per day (Nalmefene SPC, 2013).

Burden of alcohol dependence and the value of reducing consumption

Alcohol dependence places a large burden on individual health and society, which rises with increasing alcohol consumption (WHO, 2000; Rehm et al., 2003; Rehm et al., 2011). Alcohol dependence accounted for more than 70% of the overall alcohol-attributable net mortality before the age of 65 years in the European Union (Rehm and Shield, 2012). In addition to the impact on mortality, alcohol dependence is also associated with many serious social issues, including crime, family problems, parenting problems, and lost productivity in the workplace (Rehm and Shield, 2012).

Reduction of drinking, especially of heavy drinking, is associated with a reduction in alcohol-attributable harms, with the reduction being highest for the heaviest drinking category (Rehm and Roerecke, 2013). Thus, any treatment of alcohol dependence that reduces levels of consumption either to abstinence or by a reduction of heavy drinking (Rehm and Gual, 2013) can also have a significant effect on the risk of harm related to alcohol dependence.

Two types of clinical studies have been designed and are proposed by the European Medicines Agency (EMA) to assess the effect of compounds to treat alcohol dependence (EMA, 2010): relapse prevention studies and harm reduction studies. Relapse prevention studies are based on an abstinence-oriented approach, where the treatment goal is to maintain stable abstinence by prevention of relapse after withdrawal from alcohol/detoxification. Continued abstinence at the end of the active treatment period and continued abstinence until the end of the study are the primary outcomes assessed.

Harm reduction studies are based on reduction of alcohol consumption with the aim of assessing the reduction in risk of harmful consequences associated with alcohol use. A clinically significant reduced alcohol intake with subsequent harm reduction is the ultimate treatment goal of these studies.

NICE CG115 recommends a treatment goal of either abstinence or reduction of alcohol consumption, depending on the severity of alcohol dependence (NICE, 2011a). NICE CG115 also recognises that a treatment goal of alcohol reduction has clinical value for some dependent patients and may serve as an intermediate goal towards future abstinence (NICE, 2011a). Approximately half of the patients seeking help at a range of services across the United Kingdom were found to choose reduction of alcohol consumption rather than abstinence as their preferred treatment goal when asked (Heather et al., 2010).

There is an unmet need in the management of alcohol dependence, in particular for options that are more easily accessible, that encourage and motivate adherence, and that result in better treatment outcomes (Drummond et al., 2009; EMA, 2010).

Nalmefene is the only pharmacological treatment approved in Europe for the indication of reduction of alcohol consumption in patients with alcohol dependence, which can specifically be prescribed to actively drinking patients.

Licensed population

The clinical effectiveness and safety of nalmefene in patients with alcohol dependence has been demonstrated in three phase 3 randomised controlled trials (RCTs) (ESENSE1, ESENSE2, and SENSE).

These studies compared 18.06 mg nalmefene (as-needed dosing) plus the motivational and adherence-enhancing (psychosocial) intervention BRENDA with placebo (as-needed dosing) plus BRENDA. All patients had a DSM-IV diagnosis of alcohol dependence (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) and were actively drinking.

ESENSE1, ESENSE2, and SENSE were conducted in Europe and in total randomised 1,997 patients with alcohol dependence to nalmefene plus BRENDA or placebo plus BRENDA. ESENSE1 and ESENSE2 were 6-month efficacy studies, whereas SENSE was primarily designed to study the safety and tolerability of as-needed nalmefene over a 1-year period. Efficacy was added as a co-primary endpoint in the SENSE study following a protocol amendment. In ESENSE1 and ESENSE2, there were two co-primary endpoints: a reduction from baseline through month 6 in the number of heavy drinking days (HDDs) and in total alcohol consumption (TAC). These co-primary endpoints were in accordance with the recommendations in the EMA guideline on the development of medicinal products for the treatment of alcohol dependence (EMA, 2010). The EMA considers both HDD and TAC as primary variables and emphasises that a clinically relevant difference compared with placebo should be demonstrated (EMA, 2010).

Patients who considerably reduced their alcohol consumption between screening (baseline) and randomisation consumed such a small amount of alcohol at randomisation that there was little room for further improvement in alcohol consumption reduction (floor effect). Although these patients stayed in the study and maintained their low level of alcohol consumption throughout the treatment period (irrespective of treatment), it may be argued that these patients were not in need of pharmacologic treatment for the management of alcohol dependence. Furthermore, the baseline characteristics of these patients were similar to those of the total population (at screening), with no apparent features that would predict their behaviour in the period between screening and randomisation.

Therefore, after discussion with, and with the agreement of, the Scientific Advisory Group (SAG) to the EMA, post hoc analyses were performed on the subgroup of patients in all three studies with a high/very high DRL at baseline who maintained a high/very high DRL at randomisation. The purpose of these analyses was to substantiate the clinical efficacy and the clinical relevance of nalmefene and, in particular, to define the patient population who were expected to benefit most from nalmefene. The SAG recognised the validity of the subgroup analyses and the clinical effect of nalmefene; these analyses

form the basis of the nalmefene licence. Thus, the population for whom nalmefene is licensed is a subgroup of the total RCT population.

Main comparators

In line with the scope for this technology appraisal, the potential comparators for nalmefene (in conjunction with psychosocial support) are psychological intervention alone and naltrexone (in conjunction with psychosocial support).

The terms “psychosocial support,” “psychosocial intervention” and “psychological intervention” encompass a variety of different interventions and are often used interchangeably.

Psychological/psychosocial intervention

Currently, psychosocial intervention, such as extended brief intervention or motivational interviewing, is the mainstay of treatment for alcohol-dependent patients with a treatment goal of alcohol reduction (NICE, 2011a). NICE recommends psychological interventions (also termed psychosocial interventions or psychosocial support) as the preferred treatment option in alcohol-dependent patients for whom reduction of alcohol consumption is a medically relevant treatment approach and who do not require detoxification (NICE, 2011a).

A psychosocial intervention, in the form of BRENDA, was provided to all treatment groups in the three RCTs, and the efficacy results in the licensed population are presented below. It is a requirement of the nalmefene licence that all patients should be offered psychosocial support of some description (Nalmefene SPC, 2013).

Naltrexone (in conjunction with psychosocial support)

Naltrexone is available in England and Wales for the treatment of alcohol dependence and is indicated as adjunctive to psychosocial therapy with relapse prevention being the treatment goal, and is usually prescribed to patients with moderate or severe alcohol dependence who have reached abstinence following an alcohol withdrawal or detoxification process (NICE, 2011a). Unlike naltrexone, nalmefene is not indicated for patients with moderate and severe alcohol dependence who require immediate detoxification and is not indicated to maintain abstinence.

NICE CG115 makes an unlicensed recommendation for naltrexone and acamprosate in combination with psychological interventions for patients with mild alcohol dependence for whom psychological intervention alone has failed (NICE, 2011a).

Lundbeck conducted a systematic literature review to assess the efficacy of naltrexone when used in the same context of care as nalmefene (i.e., in the reduction of alcohol consumption) (see Section 6.7). Similar to the review conducted by NICE (NICE, 2011a), the Lundbeck review found limited evidence assessing naltrexone with psychosocial support in the reduction of

alcohol consumption in alcohol-dependent patients, and a conclusion could not be drawn regarding the efficacy of naltrexone with psychosocial support in this patient group. Furthermore, due to the differences in study design, inclusion/exclusion criteria, study objective, and endpoints, as well as a lack of reporting of data from the naltrexone studies, it was not possible to perform an indirect comparison of naltrexone versus nalmefene which fulfilled the requirements of good practice for evidence synthesis required by NICE (NICE, 2011b).

Clinical efficacy results

In the licensed population of patients with a high/very high DRL at baseline and randomisation, nalmefene reduced the number of HDDs and TAC statistically significantly more than placebo from baseline to month 6 in both ESENSE1 (HDD, −3.7 days/months [$P = 0.001$]; TAC, −18.3 g/day [$P < 0.001$]) and ESENSE2 (HDD, −2.7 days/months [$P = 0.025$]; TAC, −10.3 g/day [$P = 0.040$]). In both studies, the effect in favour of nalmefene was observed by month 1 and maintained throughout the study period. In the SENSE study, nalmefene significantly reduced the number of HDDs and TAC consistently more than placebo throughout the 1-year treatment period. At 1 year, the mean difference to placebo in the number of HDDs was −3.6 days/month ($P = 0.016$) and the mean difference to placebo in TAC was 17.3 g/day ($P = 0.013$) in favour of nalmefene. The difference in treatment effect between nalmefene and placebo persisted throughout the treatment period and even increased with time, indicating that tolerance to the effectiveness of nalmefene did not develop within at least 12 months of treatment.

In the pooled analysis of the two 6-month efficacy studies in the licensed population, 57% of the patients in the nalmefene group and 42% of the patients in the placebo group were classed as responders (RSDRL), which was predefined in agreement with the EMA as a two-category downward shift from baseline in DRL at month 6 ($P < 0.001$) (for patients at very high risk at baseline, RSDRL was defined as a shift to medium risk or below; for patients at high or medium risk at baseline, RSDRL was defined as a shift to low risk or below).

On the secondary endpoints, improvements were also observed in health-related quality of life (HRQL) in patients treated with nalmefene compared to placebo. The SF-36 mental component summary change from baseline to week 24 was significantly higher for the nalmefene group compared with placebo: the mean (SD) change from baseline was 5.74 (0.79) in the nalmefene group and 2.65 (0.78) in the placebo group, a mean difference of 3.09 (0.92; $P = 0.0008$). In the same way, at week 24, nalmefene had a superior effect compared with placebo in improving SF-36 physical component score (incremental of 1.23 ± 0.55; $P = 0.026$). For the EQ-5D, for the pooled analysis of the two 6-month efficacy studies in the licensed population, the mean change from baseline for nalmefene compared with placebo for the health state score and the utility index score was 3.46 points ($P = 0.0124$) and 0.03 points ($P = 0.0445$), respectively.

Reduction in alcohol consumption with nalmefene also resulted in significantly greater decreases in liver enzymes (gamma-glutamyl transpeptidase [GGT] and alanine transaminase [ALAT]).

The clinical relevance of nalmefene efficacy was demonstrated with direct evidence as analysed from the nalmefene clinical development programme and with indirect modelling evidence.

Nalmefene was generally well tolerated. The majority of the adverse events observed with nalmefene were associated with treatment initiation. These were mild or moderate in severity and appeared for a short duration. The most common adverse events associated with nalmefene were related to the central nervous system and the gastrointestinal system, which was expected from its binding profile to opioid receptors. In the licensed population, adverse events observed with the highest incidences (≥10%) in the nalmefene group compared to the placebo group were nausea (24% vs. 7%), dizziness (22% vs. 6%), insomnia (15% vs. 4%), and headache (13% vs. 10%).

Economic evaluation

A cost-effectiveness analysis was conducted for nalmefene in the treatment of alcohol dependence. The model specifically examines the ability of nalmefene in conjunction with a psychosocial intervention to reduce alcohol consumption, improve quality of life, and reduce the harmful events attributable to alcohol consumption in alcohol dependence compared with psychosocial intervention alone. A Markov model was developed for the perspective of England and considers direct medical costs attributable to alcohol treatment and alcohol-attributable harmful events. The model also considered a societal perspective on costs, including alcohol consumption's effect on cost of crime and justice.

The model consists of a short-term phase (1-year, based on the nalmefene clinical studies) and a long-term phase (beyond the initial 1-year time horizon and up to 5 years).

The model has also been structured to reflect the treatment pathway for the treatment of alcohol dependence in England. Based on NICE CG115 and expert clinical opinion in England and Wales, patients with mild alcohol dependence who fail to control their drinking levels after treatment with nalmefene + psychosocial intervention, or with psychosocial intervention alone, would likely transition to a treatment goal of abstinence and be offered acamprosate or oral naltrexone + psychosocial intervention for relapse prevention following successful alcohol withdrawal/detoxification.

The first-line comparator for nalmefene used in the cost-effectiveness assessment included in this submission is therefore psychosocial intervention alone. The submission focuses on a complete assessment of nalmefene in conjuction with psychosocial intervention as first-line treatment of patients with mild alcohol dependence.

As noted above, there is a paucity of data assessing the efficacy of naltrexone in the same context as nalmefene; that, in addition to the differences in clinical

study design, study populations, and endpoints, meant that it was not possible to perform an indirect comparison to support a cost-effectiveness assessment aligned with the NICE reference case. However, appropriate evidence is available for assessing naltrexone in maintenance of abstinence in moderate to severe alcohol dependence (NICE, 2011a). Therefore, to ensure alignment with NICE CG115 recommendations, the manufacturer integrated naltrexone into the cost-effectiveness assessment, not as a first-line comparison with nalmefene, but as second-line treatment (given the increasing severity of alcohol dependence after unsuccessful treatment via reduction for mildly dependent patients).

At a 5-year time horizon, the nalmefene strategy led to a reduction of all harmful events, avoidance of 4,857 alcohol-attributable diseases/injuries and 250 deaths per 100,000 patients versus psychosocial intervention alone. The treatment improvements also led to a larger gain of quality-adjusted life-years (QALYs) with nalmefene than with psychosocial intervention alone (0.071 QALYs) (Table 1). The results of the base-case analysis from a healthcare system perspective demonstrate that treatment with nalmefene resulted in a lower total cost and a gain in QALYs compared to psychosocial intervention alone, which is the mainstay of current clinical practice in this patient population, irrespective of care setting. Therefore, the resulting base-case incremental cost-effectiveness ratio for nalmefene + psychosocial intervention compared to psychosocial intervention alone was dominating for nalmefene, with a 100% probability of cost-effectiveness at a willingness-to-pay threshold of £20,000 per QALY gained.

Furthermore, the results of the one-way and probabilistic sensitivity analyses support this finding of cost-effectiveness and show that the conclusions are robust to alternative assumptions about model inputs.

Table 1. Base-case cost-effectiveness results

	Nalmefene + psychosocial intervention	**Psychosocial intervention alone**
Cost of medical treatment costs	£1,304	£1,165
Drug treatment–related costs	£621	n/a
Direct cost of harmful events	£821	£1,032
Cost of secondary abstinence treatment	£1,699	£2,646
Total cost	£4,445	£4,842
Difference in total cost	−£397	
QALYs	3.624	3.553
QALY difference	0.071	
ICER	Nalmefene dominates	

ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life-year.

Conclusions

In conclusion, the use of nalmefene in accordance with its licensed indication is a clinically effective and cost-effective allocation of healthcare resources in the National Health Service in England and Wales.

Nalmefene expands treatment options and addresses an unmet medical need for patients who do not require immediate detoxification and who would prefer an initial treatment goal of alcohol reduction. Moreover, these patients can be managed in a primary care/tier 2 setting, thereby increasing the proportion of dependent drinkers in the local population who enter and complete treatment in a setting appropriate to their needs, as recommended by the commissioning guidance for NICE CG115 (NICE, 2011d).

Section A – Decision problem

Manufacturers and sponsors will be requested to submit Section A in advance of the full submission (for details on timelines, see the NICE document "Guide to the single technology appraisal (STA) process" – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see Section **Error! Reference source not found.**, Appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Selincro®

Approved name: nalmefene

Therapeutic class: selective opioid receptor modulator

1.2 What is the principal mechanism of action of the technology?

Nalmefene is an opioid receptor modulator with a distinct μ, δ, and κ receptor profile. Clinical and nonclinical research suggests that alcohol intake has reinforcing properties that are, at least in part, mediated through the endogenous opioid system. In vitro studies have demonstrated that nalmefene is a selective opioid receptor ligand with antagonist activity at the μ and δ receptors and partial agonist activity at the κ receptor. In vivo studies suggest that nalmefene acts at the cortico-mesolimbic circuit to help reduce alcohol consumption (Nalmefene SPC, 2013).

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

On 25 February 2013 (EMA, 2014), the European Commission granted marketing authorisation for nalmefene for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (DRL), without physical withdrawal symptoms, and who do not require immediate detoxification. Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Nalmefene should be initiated only in patients who continue to have a high DRL 2 weeks after initial assessment (Nalmefene SPC, 2013).

A high DRL is defined by the World Health Organization (WHO) as alcohol consumption ≥ 60 g/day for men and ≥ 40 g/day for women (WHO, 2000).

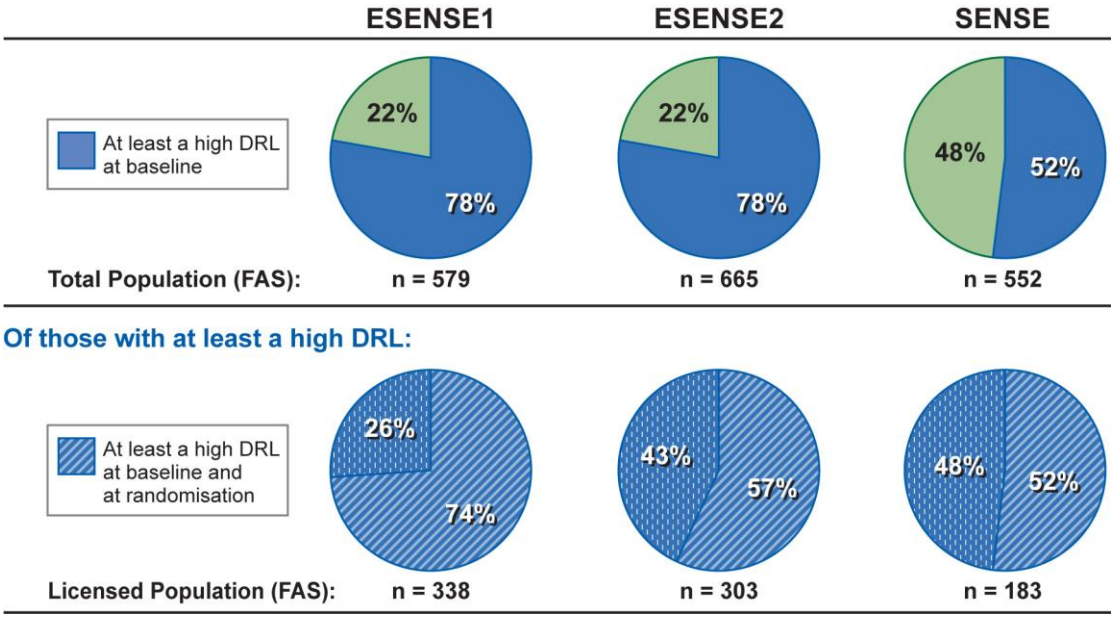
1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

There are no special conditions or circumstances attached to the marketing authorisation.

The European Medicines Agency (EMA) guideline on the development of medicinal products for the treatment of alcohol dependence was adopted in 2010 and places an emphasis on the identification of alcohol-dependent patients for whom pharmacological treatments would have the greatest benefit; and this in accordance with the disease severity and the level of alcohol consumption (EMA, 2010). The EMA Scientific Advice given to Lundbeck in 2008 (prior to the adoption of the EMA guideline on the development of medicinal products for the treatment of alcohol dependence in 2010) (EMA, 2010) placed emphasis on this need of appropriate patient identification aiming for optimal benefit from the treatment.

In alcohol treatment studies, reductions in alcohol consumption during the assessment period prior to randomisation have been observed and can have an impact on study outcomes (Epstein et al., 2005; Litten et al., 2012). This phenomenon was also observed in the three Lundbeck-sponsored randomised controlled trials (RCTs): ESENSE1, ESENSE2, and SENSE. When the data for the period between screening (baseline) and randomisation (1- to 2-week interval) were analysed, it became evident that a sizeable proportion of the patients had considerably reduced their alcohol consumption during that period (i.e., before they received any medicinal/placebo treatment intervention at randomisation). At screening (baseline), approximately 78% of the patients in ESENSE1 and ESENSE2 had a high/very high DRL, and of these, 74% of the patients in ESENSE1 and 57% of the patients in ESENSE2 maintained their high/very high DRL throughout the screening period until randomisation (Figure A1). In SENSE, approximately 52% of the patients had a high/very high DRL at baseline, of which 52% continued to have a high/very high DRL at randomisation (Figure A1).

Figure A1. Schematic overview of the patient populations in ESENSE1, ESENSE2, and SENSE



DRL = drinking risk level; FAS = full analysis set.

Patients who considerably reduced their alcohol consumption in the period between screening (baseline) and randomisation consumed such a small amount of alcohol at randomisation that there was little room for further improvement in alcohol consumption reduction (floor effect). Although these patients stayed in the study and maintained their low level of alcohol consumption throughout the treatment period, it may be argued that these patients were not in need of immediate pharmacologic treatment for the management of alcohol dependence. The baseline characteristics of these patients were similar to those of the total population (at screening), with no apparent features that would predict their behaviour in the period between screening and randomisation. This nonspecific effect leading to considerable reduction of alcohol consumption between screening and randomisation was considered to be due to motivational elements of participating in a RCT and to the screening interventions.

Therefore, after discussion with, and with the agreement of, the Scientific Advisory Group (SAG) to the EMA, post hoc subgroup analyses were performed to substantiate the clinical efficacy and the clinical relevance of nalmefene effect, most particularly in order to define a population in which the benefit of nalmefene would be greatest. The licensed population from the nalmefene clinical trials was defined post hoc as the patients with a high or very high DRL at screening and randomisation. In this post hoc population, the treatment effect was larger than in the total clinical trial population (which included patients with medium DRLs for ESENSE1 and ESENSE2, medium and low DRLs for SENSE, and patients who reduced their alcohol consumption after initial assessment prior to the randomisation visit).

Lundbeck thus proposed that the marketing authorisation be restricted to the defined post hoc licensed population, as these were the patients who would

benefit most from nalmefene. This was aligned with the EMA guideline on the development of medicinal products for the treatment of alcohol dependence (EMA, 2010), which was published after initiation of nalmefene trials and considers and emphasises that alcohol-dependent patients in high need of treatment are those with a high or a very high DRL.

During the regulatory process, the SAG to the EMA confirmed that the effect size of nalmefene was clinically meaningful for the post hoc population (EMA, 2012). The net difference over placebo in the change from baseline to month 6 in HDD was −3.7 days/month in ESENSE1 ($P < 0.001$) and −2.7 days/month in ESENSE2 ($P = 0.025$); the net difference of nalmefene over placebo in the change from baseline to month in TAC was −18.3 g/day in ESENSE1 ($P < 0.001$) and −10.3 g/day in ESENSE2 ($P = 0.04$) (EMA, 2012) (see Section 6.5). The SAG also recognised the validity of the post hoc analysis defining the licensed population. Whilst it was acknowledged that post hoc analyses are not ideal, it was noted that they are commonly used in clinical trials for psychiatric drugs, given the high dropout rates encountered in these populations. The SAG also confirmed that the study population is representative of the population for whom nalmefene is proposed to be prescribed. Based on the data provided, patients with high and very high DRL are more likely to be the licensed population who could benefit from nalmefene treatment, and the SAG "emphasized that the therapeutic indications should clearly instruct physicians (including general practitioners) to easily recognise the patients who could be the target of the drug" (EMA, 2012).

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Nalmefene is indicated in the UK:

> "for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high DRL,[1] without physical withdrawal symptoms, and who do not require immediate detoxification.
>
> "Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.
>
> "Nalmefene should be initiated only in patients who continue to have a high DRL 2 weeks after initial assessment."

That is, nalmefene is indicated in patients who have not reduced their drinking or who continue to drink more than 7.5 units a day (men) or 5 units a day (women).

[1] A high DRL is defined by the World Health Organization (WHO) as alcohol consumption ≥ 60 g/day for men and ≥ 40 g/day for women (WHO, 2000).

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The efficacy and tolerability of nalmefene in the treatment of alcohol dependence within its approved indication were evaluated in three phase 3 RCTs sponsored by Lundbeck: ESENSE1, ESENSE2, and SENSE.

Previously, five studies in alcohol-use disorders were conducted by Biotie Therapies Corporation (hereafter referred to as Biotie). As part of a development programme for nalmefene, these studies suggested that nalmefene could be effective in reducing alcohol consumption and provided the rationale for the further development of the nalmefene 18 mg dose (EMA, 2012). These studies were considered by the EMA during the regulatory process only to support nalmefene development to its current indication, as the design and context of these studies were not aligned with the licensed indication for nalmefene (EMA, 2012). **Error! Reference source not found.** (Section **Error! Reference source not found.**) details these studies and the reason why they are not relevant to the decision problem addressed by this submission.

Table A1 presents a summary of completed phase 3 studies investigating nalmefene in adults with alcohol dependence diagnosed according to DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), and from which the efficacy of the compound for its licensed population was derived.

Table A1. List of completed trials of nalmefene in adults with alcohol dependence (DSM-IV-TR criteria)

Trial acronym (NCT number) and phase	Trial design	Interventions	Population	Primary outcome measures	Secondary outcome measures	Reference
ESENSE1 (NCT00811720) Phase 3	Randomised, double-blind, placebo-controlled, parallel-group study	Nalmefene 18 mg, as-needed use, tablets, orally, 6 months Placebo, as-needed use, tablets, orally, 6 months	Patients aged ≥ 18 years with a primary diagnosis of alcohol dependence according to DSM-IV-TR criteria; ≥ 6 HDDs in the 4 weeks preceding the screening visit; an average alcohol consumption at WHO medium risk level or above in the 4 weeks preceding the screening visit	Change from baseline in the monthly number of HDDs[a] Change from baseline in the monthly TAC[b]	RSDRL response[c] Change from baseline in clinical status using CGI-S[d] Change in clinical status using CGI-I[e] Liver function tests: GGT, ALAT values	Mann et al., 2013; van den Brink et al., 2013[f]; Keating, 2013[g]
ESENSE2 (NCT00812461) Phase 3	Randomised, double-blind, placebo-controlled, parallel-group study	Nalmefene 18 mg, as-needed use, tablets, orally, 6 months Placebo, as-needed use, tablets, orally, 6 months	Patients aged ≥ 18 years with a primary diagnosis of alcohol dependence according to DSM-IV-TR criteria; ≥ 6 HDDs in the 4 weeks preceding the screening visit; an average alcohol consumption at WHO medium risk level or above in the 4 weeks preceding the screening visit	Change from baseline in the monthly number of HDDs[a] Change from baseline in the monthly TAC[b]	RSDRL response[c] Change from baseline in clinical status using CGI-S[d] Change in clinical status using CGI-I[e] Liver function tests: GGT, ALAT values	Gual et al., 2013; van den Brink et al., 2013[f]; Keating, 2013[g]
SENSE (NCT00811941) Phase 3	Randomised, double-blind, placebo-controlled, parallel-group, 52-week study	Nalmefene 18 mg, as needed, orally, 52 weeks Placebo, as needed, orally, 52 weeks	Patients aged ≥ 18 years with alcohol dependence diagnosed according to DSM-IV-TR	Long-term safety and tolerability (adverse events, clinical safety laboratory tests and vital signs) Alcohol consumption by the monthly number of HDDs Monthly TAC	Proportion of responders based on drinking measures Alcohol dependence symptoms and clinical status Liver function and other biological laboratory tests Pharmacoeconomic outcomes Long-term therapeutic effect of treatment on reduction of alcohol	van den Brink et al., 2012; Keating, 2013[g]

Trial acronym (NCT number) and phase	Trial design	Interventions	Population	Primary outcome measures	Secondary outcome measures	Reference
					consumption Long-term therapeutic effect of treatment on alcohol dependence symptoms and clinical status Long-term therapeutic effect of treatment on liver function and other biological tests Long-term therapeutic effect of treatment on pharmacoeconomic outcomes	

ALAT = alanine aminotransferase; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; CGI-I = Clinical Global Impression-Global Improvement; CGI-S = Clinical Global Impression-Severity; GGT = gamma-glutamyl transferase; HDD = heavy drinking day; NCT = National Clinical Trial; RSDRL = response defined as a downward shift from baseline in drinking risk level by two risk categories; TAC = total alcohol consumption; WHO = World Health Organization.

[a] One HDD was defined as a day with alcohol consumption ≥ 60 g for men and ≥ 40 g for women.

[b] TAC was defined as mean daily alcohol consumption in g/day over a month (28 days).

[c] RSDRL response was defined as a downward shift from baseline in drinking risk level: for patients at very high risk at baseline, a shift to medium risk or below, and for patients at high or medium risk at baseline, a shift to low risk or below.

[d] The CGI-S provides the clinician's impression of the patient's current state of mental illness. The clinician uses his or her clinical experience of this patient population to rate the severity of the patient's current mental illness on a 7-point scale ranging from 1 (normal – not at all ill) to 7 (among the most extremely ill patients).

[e] The CGI-I provides the clinician's impression of the patient's improvement (or worsening). The clinician assesses the patient's condition relative to a baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

[f] Post hoc analysis of the efficacy, safety, and tolerability of as-needed nalmefene in the pooled subgroup of patients with at least a high drinking level from ESENSE1 (NCT00811720) and ESENSE2 (NCT00812461).

[g] Review of efficacy and tolerability of as-needed nalmefene as demonstrated in the pivotal randomised phase 3 studies ESENSE1, ESENSE2, and SENSE.

Sources: Clinicaltrials.gov; Gual et al., 2013; van den Brink et al., 2013; Keating, 2013.

With respect to ongoing studies, Lundbeck is currently conducting the following studies:

- An interventional, single-site, open-label, four-group, single-dose study investigating the pharmacokinetic properties of nalmefene in patients with renal impairment (mild, moderate, or severe) and in healthy subjects. The study will recruit 32 subjects. This study was defined in the additional pharmacovigilance activities of the risk management plan (agreed with the Committee for Medicinal Products for Human Use [CHMP] of the EMA and approved by the Pharmacovigilance Risk Assessment Committee [PRAC]). The report is expected in Quarter 1, 2014.
- An 18-month post-authorisation safety study (PASS). This is a 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. 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 PAS register (ENCEPP/SDPP/5678).
- A non-interventional prospective longitudinal cohort study of patients with alcohol dependence initiating treatment 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. The first patient‘s first visit was performed in Q4 2013.
- An exploratory, interventional, open-label, fixed-dose study with Selincro® as-needed use in alcohol-dependent patients with liver impairment. A 12-week study, conducted versus planned in Germany. Main exploratory endpoints are reduction in alcohol consumption and change in liver stiffness. The study will recruit 60 subjects. The first patient‘s first visit is expected in Q3 2014. Recruitment period is 6 months.
- An interventional, open-label study of 18 mg Selincro® as-needed use in the treatment of patients with alcohol dependence in primary care. A 12-week study, planned in 5 European countries. The primary objective is to determine the reduction in alcohol consumption of Selincro® in conjunction with continuous psychosocial support in primary care. The study will recruit 635 subjects. The first subject is expected in Q3 2014. Recruitment period is 12 months.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The UK launch of nalmefene was on 7 May 2013.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Nalmefene is licensed throughout the EU. No other regulatory approval is expected outside the UK before the end of February 2014.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

The Scottish Medicines Consortium (SMC) has accepted nalmefene for use within National Health Service (NHS) Scotland in accordance with its licensed indication. This advice was published on 7 October 2013 (SMC, 2013).

Following a full submission, the All Wales Medicines Strategy Group (AWMSG) approved nalmefene for use in NHS Wales on 15 January 2014, in accordance with its licensed indication. Confirmation of Ministerial ratification was received on 26 February 2014.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A2. Unit costs of technology being appraised

Pharmaceutical formulation	Nalmefene 18 mg film-coated tablets available in 14-tablet pack or 28-tablet pack.
Acquisition cost (excluding VAT)	The Department of Health has approved a UK nalmefene price of £3.03 per tablet.[a] The price of the 14-tablet pack is £42.42; the price of the 28-tablet pack is £84.84.[a]
Method of administration	Nalmefene is for oral use.
Dose	Nalmefene is to be taken as-needed: on each day the patient perceives a risk of drinking alcohol, 1 tablet should be taken, preferably 1-2 hours prior to the anticipated time of drinking. If the patient has started drinking alcohol without taking nalmefene, the patient should take 1 tablet as soon as possible. The maximum dose of nalmefene is 1 tablet per day.
Dosing frequency	One tablet on each day the patient perceives a risk of drinking alcohol (as-needed dosing).
Average length of a course of treatment	In clinical practice, the patient's response to treatment and the need for continued pharmacotherapy should be evaluated on a regular basis (e.g., monthly). The physician should continue to assess the patient's progress in reducing alcohol consumption, overall functioning, treatment adherence, and any potential side effects. Clinical data for the use of nalmefene under randomised controlled conditions are available for up to 12 months. Caution is advised if nalmefene is prescribed for more than 1 year (Nalmefene SPC, 2013).

Average cost of a course of treatment	In pooled analyses of the licensed population from the three nalmefene pivotal studies (ESENSE1, ESENSE2, and SENSE), patients in the nalmefene group took medication on an average of 56% of the days (58% in the pooled ESENSE1 and ESENSE2 population) (calculated by dividing the number of days of intake per individual patient by the number of days the patient was in the trial [until dropout or end of study]), or an average of 35% of the days (calculated by dividing the number of days of intake per individual patient by the full study period). In assessing the performance of nalmefene from a health economic perspective, Lundbeck considered the trial predefined time horizon for calculation of nalmefene's average annual drug cost per patient (35% of the days). Thus, the average annual cost per patient was estimated to be £385. Assuming 56% intake, the maximum cost per patient per year would be £620.
Anticipated average interval between courses of treatments	Although it is anticipated that a patient could be prescribed nalmefene for more than one treatment course (following a recurrence or resumption of high DRL consumption levels), clinical data for the use of nalmefene under randomised controlled conditions are available for a period of 6 to 12 months only. For patients responding to nalmefene treatment, no data are currently available in terms of maintenance of effect beyond 12 months.
Anticipated number of repeat courses of treatments	Repeat courses are anticipated to be dependent on patient response to treatment. The summary of product characteristics states that caution should be exercised when using nalmefene for more than 12 months.
Dose adjustments	No dose adjustments are required through the course of the treatment or for any special patient populations.
[a] 2013 prices.	

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests or ongoing monitoring of patients will be needed. Tools for the assessment of alcohol dependence are already available and in use in clinical practice across England and Wales.

The nalmefene summary of product characteristics (SPC) states that at an initial visit, the patient's clinical status, alcohol dependence, and level of alcohol consumption (based on patient reporting) should be evaluated. Thereafter, the patient should be asked to record his or her alcohol consumption for approximately 2 weeks. There is existing guidance and a number of validated simple assessment tools recommended in NICE public health guidance PH24 and NICE Clinical Guideline (CG) 115 (e.g., Alcohol Use Disorders Identification Test [AUDIT], Severity of Alcohol Dependence Questionnaire [SADQ], Leeds Dependence Questionnaire [LDQ]) that are

suitable to assess consumption, dependence, and need for assisted withdrawal (detoxification); all components should be assessed for the correct identification of the patients for which nalmefene in indicated.

At the next visit, nalmefene may be initiated in patients who continued to have a high DRL over this 2-week period, in conjunction with psychosocial intervention focused on treatment adherence and reducing alcohol consumption (Nalmefene SPC, 2013). Nalmefene does not require specialist initiation. It can be both initiated and used in primary care and community settings without any requirement for additional testing beyond what is usually performed for patients diagnosed with alcohol dependence. The SAG consulted by the EMA also endorsed the prescribing of nalmefene by general practitioners (GPs). This allows patients to access treatment in a setting appropriate to their needs and circumstances.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No monitoring of patients is required over and above usual clinical practice with nalmefene.

Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. The patient's response to treatment and the need for continued pharmacotherapy should be evaluated on a regular (e.g., monthly) basis (Nalmefene SPC, 2013), which is routine clinical practice in the management of chronic conditions in primary care.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

In common with all other pharmacological agents used in the management of alcohol dependence, nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption (Nalmefene SPC, 2013).

The term "psychosocial support" covers a broad spectrum of interventions, but the important elements for effective psychosocial interventions are a common set of interventions aimed at helping patients identify problems associated with their alcohol dependence, gauging their readiness to change and their perceptions of their own abilities, and providing a supportive, non-judgemental relationship through the change process (Rome, 2014a).

These components can be delivered by primary care practitioners with support from local community-based non-statutory alcohol services (Rome, 2014a).

During the nalmefene pivotal trials, the psychosocial intervention used at each visit from randomisation was BRENDA[2] (Starosta et al., 2006). BRENDA was used in accordance with the EMA guideline on the development of medicinal products for the treatment of alcohol dependence, which states that standardised psychosocial interventions should be allowed in alcohol dependence studies and kept to a constant and low level for all patients (EMA, 2010). BRENDA is a framework or approach consisting of six components and was developed for use in combination with addiction pharmacotherapy to enhance medication adherence; however, none of the BRENDA components are specific to any one illness (Starosta et al., 2006). Many of these components are not unique to alcohol dependence and are employed routinely in general practice (Rome, 2014b).

Continuous psychosocial support indicated with the use of nalmefene refers to a psychosocial intervention focused on treatment adherence and reducing alcohol consumption (Nalmefene SPC, 2013). It is a patient-centred approach aimed at supporting the patient to succeed in making changes and emphasising the importance of adherence to treatment by providing positive feedback and help in solving difficulties with adherence (Volpicelli et al., 2001; Johnson et al., 2003; Pettinati et al., 2004; Pettinati et al., 2005; Starosta et al., 2006).

In real life, such an intervention starts with an initial assessment of the patient's health status, alcohol consumption, and related problems (e.g., by focused history, examination, blood tests, or a brief screening tool). The results are reported and discussed with the patient, and advice to change the drinking level and pattern is given. This initial phase aims to create and facilitate a therapeutic relationship, motivate the patient to change his or her drinking behaviour, or further enhance the patient's motivation to reach his or her treatment goal.

The follow-up visits consist of motivational support to reinforce and support continued adherence to treatment goals and medication. The clinician monitors patient health, blood test results, and drinking status, with empathic understanding, positive feedback, and recommendations on how to further motivate the patient to reach or maintain his or her treatment goal.

Healthcare providers in primary care and tier 2 services already address a wide variety of behavioural problems in their patients and routinely manage chronic conditions (e.g., diabetes) with a combination of clinical advice and medication management. Therefore, the framework for providing these interventions will be familiar to primary care practitioners as being common to other behavioural approaches in the management of long-term conditions, with common stages of assessment, planning, delivery of intervention, and evaluation (Rome, 2014a). Following initial biopsychosocial evaluation, these stages will be revisited as necessary over a period of weeks or months, depending on clinical presentation, but should be managed within 10- to

2 Biopsychosocial evaluation, Report to the patient on assessment, Empathic understanding of the patient's situation, Needs collaboratively identified by the patient and treatment provider, Direct advice to the patient on how to meet those needs, Assess reaction of the patient to advice and adjust as necessary for best care.

15-minute sessions and can therefore be accommodated within the time constraints of general practice appointments.

Thus, the psychosocial support recommended with the use of nalmefene can be delivered during a routine consultation by a GP or other healthcare professional in a primary care/tier 2 or tier 3 setting.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

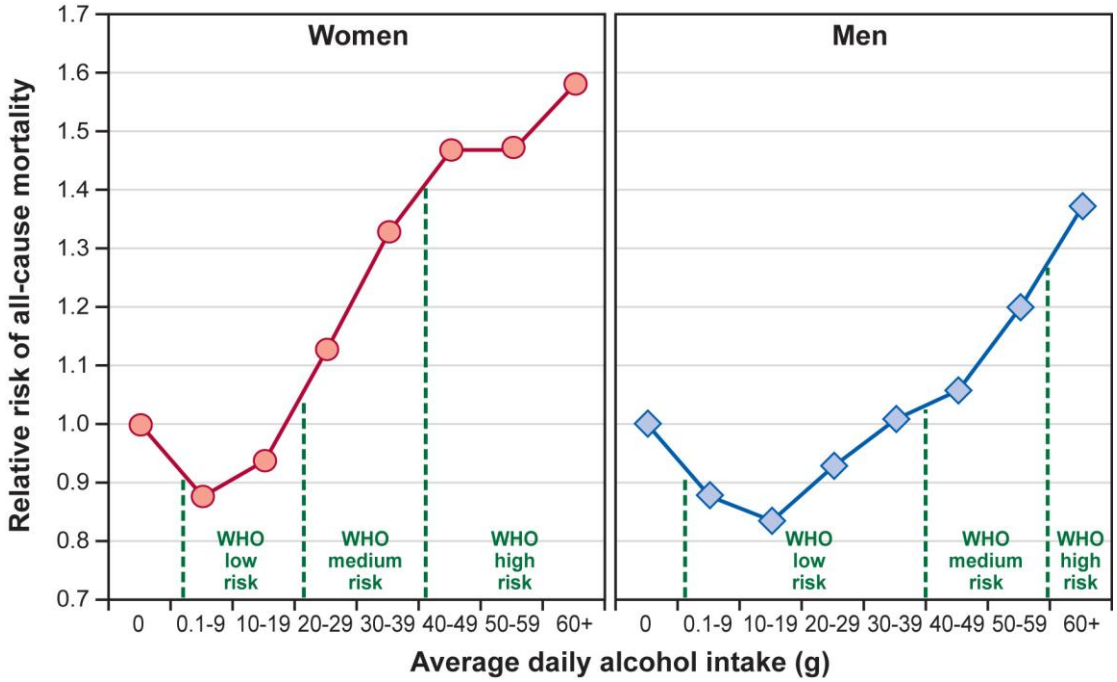
2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

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. The development of alcohol dependence is contingent on the degree to which a range of genetic, environmental, and psychological risk factors interact in any given individual who consumes alcohol (Gottesman and Gould, 2003; Nestler, 2000; Heilig et al., 2011; Bierut, 2011). A central characteristic of the dependence syndrome is the desire (often strong and sometimes perceived as overpowering) to drink alcohol, and patients with alcohol dependence have difficulty limiting consumption (WHO, 1992). Alcohol dependence has a high probability of a chronic and progressive course.

Different classification systems can be used to define alcohol dependence: the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (American Psychiatric Association [APA], 2013) and the *International Statistical Classification of Diseases and Related Health Problems, 10th Version* (ICD-10) (WHO, 1993). The fifth edition of the DSM (DSM-5) was launched in 2013. Whereas the fourth edition of the DSM (DSM-IV) had separate categories for alcohol “abuse” and “dependence,” the DSM-5 combines them into a single category, termed “alcohol-use disorder” (APA, 2013). The definition has been expanded to comprise 11 diagnostic criteria (including “craving”), and depending on the number of criteria met, the patient is placed on a continuum of disease severity, from mild to severe (APA, 2013). These revisions are intended to avoid problems of distinction between abuse and dependence and to better reflect the symptoms experienced by patients (APA, 2013). However, the DSM-5 definition is not expected to increase diagnosis rates—a 95.2% agreement between diagnoses of alcohol abuse or dependence under DSM-IV and DSM-5 has been observed (Peer et al., 2013).

Alcohol dependence places a large burden on individual health and society, which rises with increasing alcohol consumption (WHO, 2000; Rehm et al., 2003; Rehm et al., 2011). 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 (Rehm and Shield, 2012). As shown in Figure A2, the relative risk for all-cause mortality is highest among patients with the highest average daily intake of alcohol. 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 (Rehm and Shield, 2012).

Figure A2. Relative risk for all-cause mortality by average daily intake of alcohol



WHO = World Health Organization.

Source: Adapted from English et al., 1995.

Estimates of the overall prevalence of alcohol dependence in England vary from approximately 4% to 6% (Drummond et al., 2005; NICE, 2011a; Fuller et al., 2009). Of the estimated 1.6 million people who are alcohol dependent in England, only approximately 6% per year receive treatment (McManus et al., 2009; Alcohol Concern, 2010). 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 (NICE, 2011a).

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 (Figure A3) (Rehm and Roerecke, 2013). As shown in Figure A3, a reduction of 3 drinks or 36 grams of pure alcohol per day from a baseline of 96 grams results in a reduced mortality risk of 119 per 10,000; a similar reduction of 36 grams from a baseline of 60 grams per day results in a reduced mortality risk of 38 per 10,000.

Reduction of alcohol consumption as a clinically significant treatment goal is widely accepted in current literature reports (van den Brink et al., 2008; van Amsterdam and van den Brink, 2013; EMA, 2012). Reduction of alcohol consumption, as an integrated part of the continuum of treatment for alcohol dependence, is an alternative option for patients who do not want to consider abstinence as an initial treatment goal and who do not require immediate detoxification. Approximately half of the patients seeking help at a range of services across the United Kingdom were found to choose reduction of

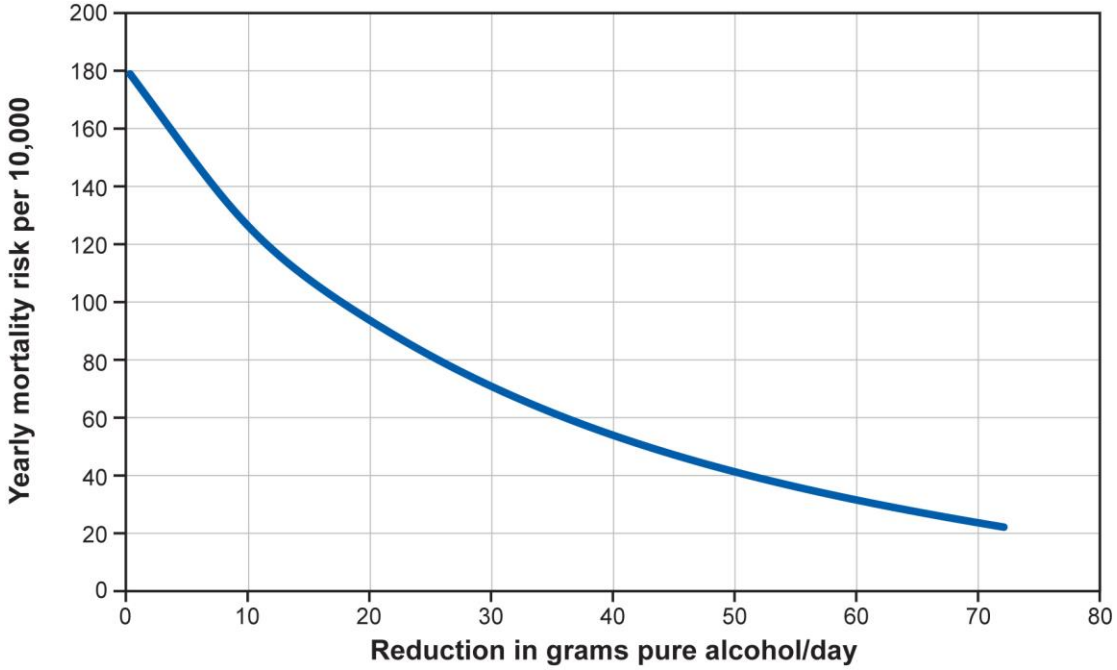
alcohol consumption rather than abstinence as their preferred treatment goal when asked (Heather et al., 2010). There is also evidence that achieving a successful outcome of abstinence or reduction is related to initial goal preference, and allowing patients to set their own treatment goal is associated with a higher chance of success, regardless of preference (Adamson et al., 2010; Orford and Keddie, 1986). Treatment of alcohol dependence reduces levels of consumption either to abstinence or by a sizable reduction of heavy drinking (Rehm and Gual, 2013).

NICE CG115 recommends a treatment goal of either abstinence or reduction of alcohol consumption, depending on the severity of alcohol dependence (NICE, 2011a).

Although most patients with an alcohol use disorder identified by GPs in England are believed to need specialist treatment, qualitative research suggests many are not referred because of perceived difficulties in access (with waiting lists for specialist treatment being the main reason given) and patient preference not to engage in specialist treatment (Drummond et al., 2005).

There is an unmet need in the management of alcohol dependence, in particular for options that are more easily accessible, that encourage and motivate adherence, and that result in better treatment outcomes (Drummond et al., 2009; EMA, 2010). Psychosocial intervention, such as extended brief intervention or motivational interviewing, is the mainstay of treatment for alcohol-dependence and has been shown to be effective in both reducing alcohol consumption and maintaining abstinence (NICE, 2011a; EMA, 2010).

Figure A3. Reduction of alcohol intake in heavy drinkers and associated mortality risk reduction



Source: Rehm and Roerecke, 2013.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

The manufacturer has estimated that the following numbers of patients are covered by the indication described in Section 1.1 and would be potentially eligible for treatment with nalmefene according to its SPC. There are no other indications for this technology:

- Year 1 583,732 England + 2,015 Wales = 585,747
- Year 2 588,739 England + 2,700 Wales = 591,439
- Year 3 593,789 England + 3,392 Wales = 597,181
- Year 4 598,883 England + 4,091 Wales = 602,974
- Year 5 604,020 England + 4,798 Wales = 608,818

Mid-year population estimates for England and Wales were taken from the Office for National Statistics and adjusted to give a total population aged 18 years or older. The prevalence of alcohol dependence in England and Wales was assumed to be 5.9% (Fuller et al., 2009).

As per NICE CG115, 84% of those adults with alcohol dependence were assumed to have mild alcohol dependence (NICE, 2001a), of which 29% were assumed to have high or very high DRL, both at initial assessment and 2 weeks later (in accordance with the requirements of the nalmefene licence).

Further details are given in Section 8.1.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

In the United Kingdom in 2004, the age-standardised mortality due to alcohol dependence for people aged 15 to 64 years was 1.28 per 100,000 people (Rehm and Shield, 2012). The disability-adjusted life-years and potential years of life lost were 562.9 and 23.1 per 100,000 people, respectively (Rehm and Shield, 2012). It is assumed that life expectancy in England and Wales would be consistent with the UK rates reported by Rehm and Shield (2012).

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Table A3 summarises all guidance on alcohol-use disorders issued by NICE and the subgroups considered. However, the patient populations covered by NICE Clinical Guidelines 100 and 120 fall outside of the nalmefene licence and are therefore not considered relevant to the decision problem addressed in this submission.

Table A3. Guidance on alcohol-use disorder issued by NICE and the subgroups addressed

Guideline	Issue Date	Subgroups Considered
Public Health Quality Standard on alcohol	In development	N/A
Clinical Guideline CG115 Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence	February 2011	Mild alcohol dependence, moderate and severe alcohol dependence after successful withdrawal
Clinical Guideline CG120 Psychosis with coexisting substance misuse	March 2011	Patients with psychosis and coexisting substance abuse
Clinical Guideline CG100 Alcohol-use disorders: diagnosis and clinical management of alcohol-related physical complications	June 2010	Adults and young people (aged ≥ 10 years) with acute alcohol withdrawal (including seizures and delirium tremens), Wernicke's encephalopathy, liver disease, and acute and chronic pancreatitis
Public health guidance PH24 Alcohol-use disorders: preventing harmful drinking	June 2010	N/A
Quality Standard QS11 Alcohol dependence and harmful alcohol use quality standard	August 2011	N/A
CG = clinical guideline; N/A = not applicable; PH = public health; QS = quality standard.		

In this submission, based on the marketing authorisation for nalmefene, the subpopulation of patients with alcohol dependence for whom nalmefene is suitable has already been determined by the EMA. The nalmefene licence only covers a subgroup of patients, namely, adults with alcohol dependence who have a high DRL without physical withdrawal symptoms and who do not require immediate detoxification (who continue to have a high DRL 2 weeks after initial assessment). These patients' alcohol dependence would be equivalent to the NICE definition of "mild" in CG115 (NICE, 2011a).

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Psychosocial intervention is the mainstay of treatment for alcohol dependence irrespective of care setting and has been shown to be effective in reducing alcohol consumption (NICE, 2011a). Figure A4 depicts the treatment that Lundbeck understands to be current clinical practice in England and Wales for patients with alcohol dependence. Figure A5 depicts where nalmefene might be positioned for alcohol-dependent patients. The introduction of nalmefene to treat mildly alcohol-dependent patients allows the existing pathway described

in NICE CG115 to be delivered in a primary care/tier 2 setting, thereby increasing the proportion of dependent drinkers in the local population who enter and complete treatment in a setting appropriate to their needs, as recommended by the commissioning guidance (NICE, 2011d).

Figure A4 shows that following an initial diagnosis of alcohol dependence, confirmed by the Alcohol Use Disorders Identification Test (AUDIT), the patient is initially offered a brief intervention. The treating physician also determines whether the patient needs immediate detoxification/assisted alcohol withdrawal. Depending upon the decision made, the patient will then follow either the left-hand “path” or the right-hand “path” as depicted in Figure A4 and Figure A5.

(i) Patients not requiring detoxification or assisted withdrawal: mild alcohol dependence

Patients with alcohol dependence who do not require immediate detoxification may be suitable for a different management strategy, one of reduction of alcohol consumption (Figure A4 and Figure A5). These are the patients for whom nalmefene is indicated. These patients are commonly seen in a primary care setting, which is a setting more appropriate to the needs of this patient group, as recommended by the commissioning guidance for NICE CG115 (NICE, 2011d).They are readily recognised by clinicians as individuals who know they are consuming too much alcohol as a result of negative consequences, and they have frequently intended or attempted to reduce their drinking, but continue to drink at harmful or high-risk levels (Expert opinion, Lundbeck Data on File, 2014).

NICE CG115 recognises that a treatment goal of alcohol reduction has clinical value for some dependent patients and may serve as an intermediate goal towards future abstinence. The NICE guidelines define this population as having “mild dependence.” Patients with mild alcohol dependence are generally suitable for a treatment goal of reduction of consumption instead of abstinence. The severity level of alcohol dependence of included subjects in the nalmefene clinical phase 3 programme was low (Alcohol Dependence Scale [ADS][3] score 13.6) (EMA, 2012). According to NICE CG115, most patients with mild alcohol dependence will not require immediate detoxification and will not have physical withdrawal symptoms (NICE, 2011a).

Until now, there has been no pharmacologic agent licensed for the reduction of alcohol consumption, and psychosocial intervention has been the mainstay of current treatment for patients with mild alcohol dependence who do not require detoxification and have no physical withdrawal symptoms. Patients with mild alcohol dependence who continue to have a high DRL and no physical withdrawal symptoms following a 2-week assessment period will now be eligible for treatment with nalmefene within its licensed indication in conjunction with psychosocial intervention. The 2-week assessment period

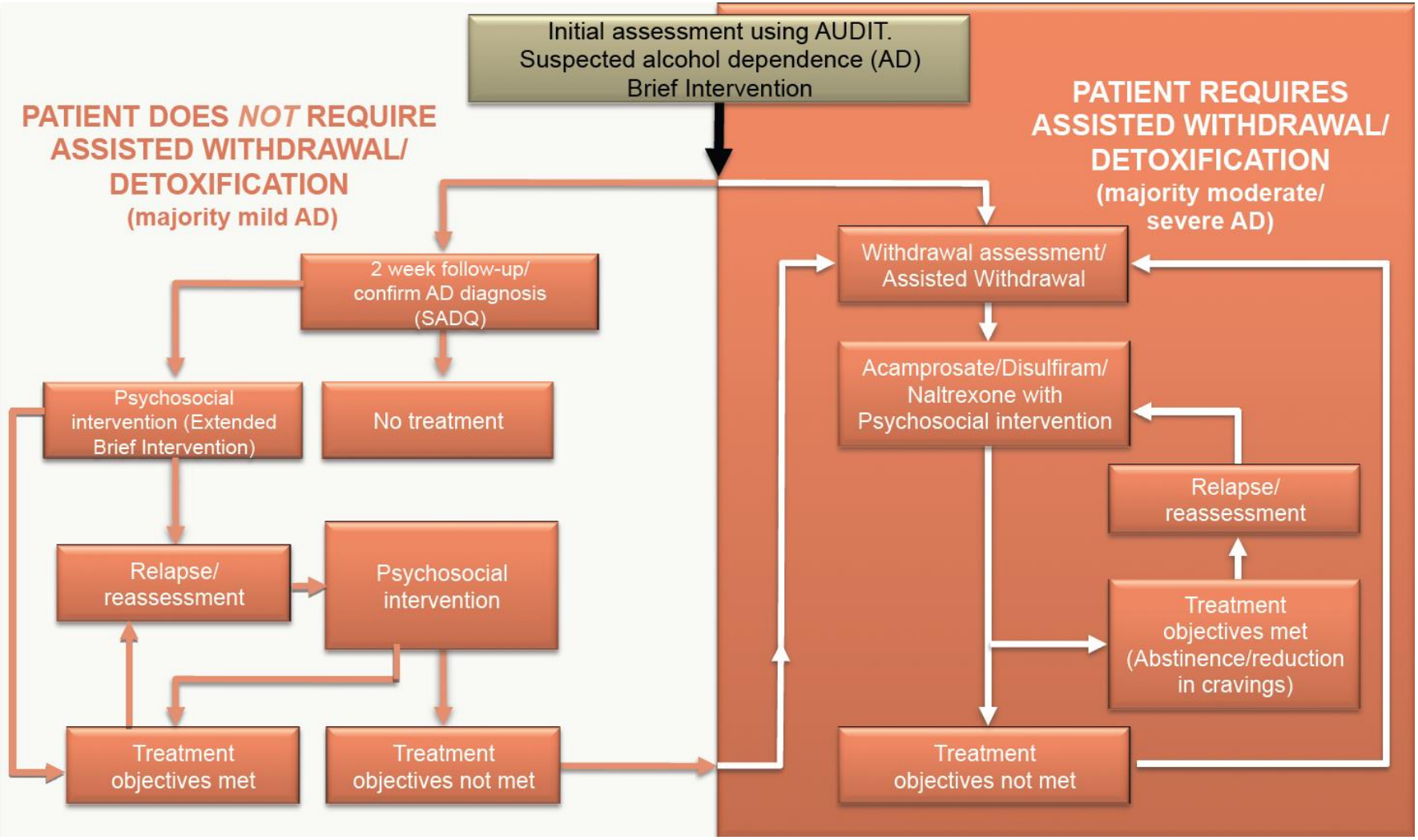
3 ADS total score is 25 items covering alcohol withdrawal symptoms, impaired control over drinking, awareness of a compulsion to drink, increased tolerance to alcohol, and drink-seeking behaviour.

allows the physician to optimise patient selection according to the patients who would be expected to derive a benefit from nalmefene treatment.

Moreover, nalmefene does not require specialist initiation and can be used in a primary care setting (Nalmefene SPC, 2013; Expert opinion, Lundbeck Data on File, 2014). As a consequence, the introduction of nalmefene enables the current treatment paradigm or pathway described in NICE CG115 to be delivered in a primary care/tier 2 setting without the need for specialist referral, expanding the available treatment options for patients with mild alcohol dependence and delivering care in a treatment setting suited to their particular needs, as recommended by the commissioning guidance (NICE, 2011d).

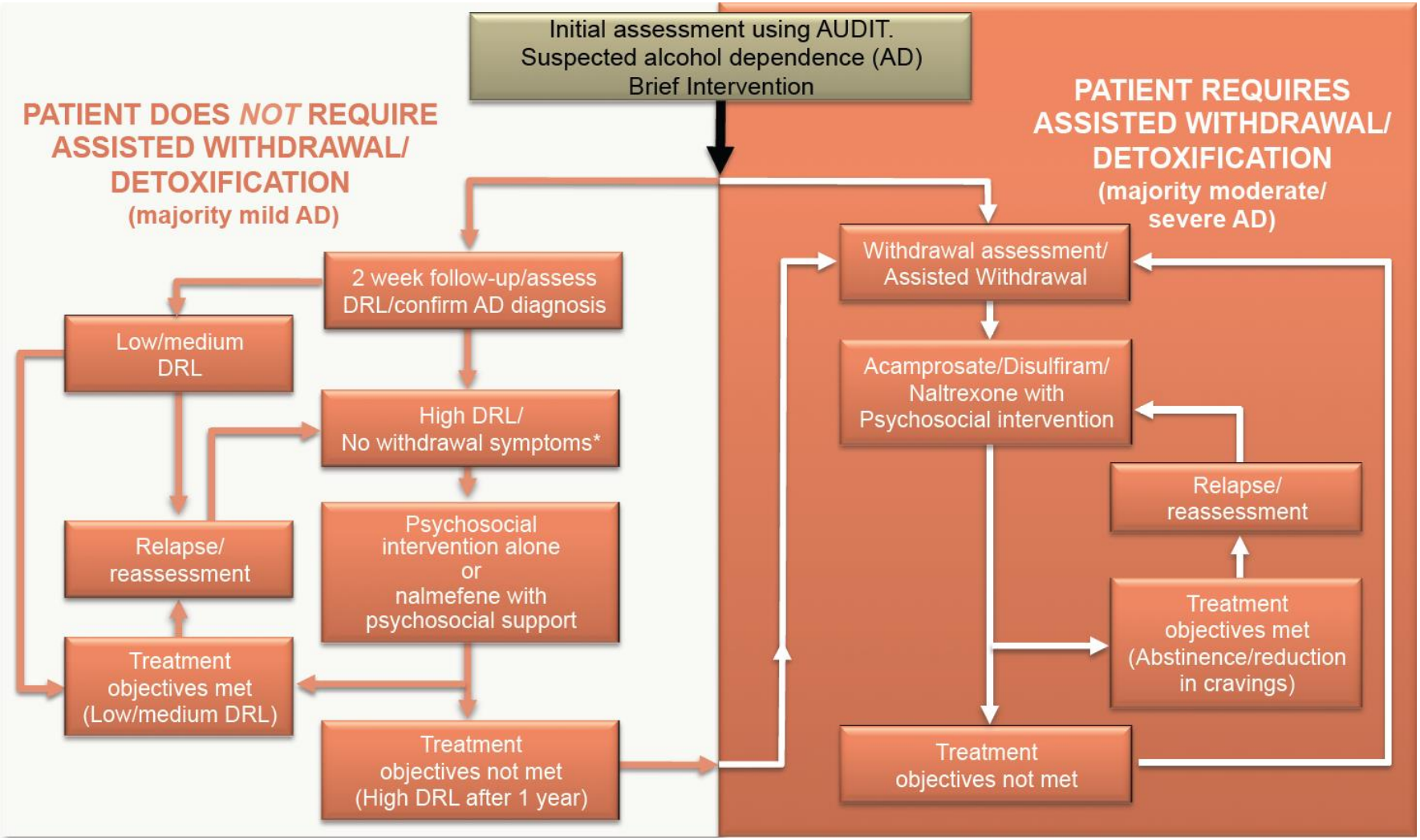
In terms of treatment course duration, clinical data for the use of nalmefene under randomised controlled conditions are available for a period of 6 to 12 months only. Therefore, caution is advised if nalmefene is prescribed for more than 1 year. If a patient continued to have high DRL at the end of a 12-month period, Lundbeck would expect the physician to switch that patient to a treatment goal of abstinence.

Figure A4. Schematic of current clinical practice for the management of alcohol dependence in England and Wales



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

Figure A5. Schematic of proposed positioning for nalmefene within clinical practice in England and Wales



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.

(ii) Patients needing detoxification: moderate and severe alcohol dependence

The management pathway for patients with moderate and severe alcohol dependence is shown on the right-hand side of Figure A4. 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 an assisted alcohol withdrawal programme. After successful completion of the alcohol withdrawal programme, the physician may consider pharmacotherapy to assist in maintaining abstinence (NICE, 2011a).

Acamprosate is licensed for use in patients specifically to help maintain abstinence (Acamprosate [Campral] SPC, 2011). Disulfiram, described as an alcohol deterrent compound, is licensed as an adjuvant in the treatment of carefully selected and cooperative patients with drinking problems (Disulfiram [Antabuse] SPC, 2011). As such, neither acamprosate nor disulfiram is licensed in the indication under consideration in this submission.

Naltrexone is recommended in NICE CG115 for the treatment of alcohol dependence; however, naltrexone was not licensed in England for this patient population when NICE CG115 was published in February 2011 (NICE, 2011a). Two versions of naltrexone 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 (Naltrexone SPC, 2010). 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 (Adepend SPC, 2013). It is not specifically licensed for the reduction of consumption in people with alcohol dependence. Figure A4 presents the use of these therapies in combination with appropriate psychosocial intervention in patients with moderate and severe alcohol dependence.

Nalmefene is not indicated for patients with moderate and severe alcohol dependence who require immediate detoxification and is not indicated to help achieve or maintain abstinence. As a consequence, the introduction of nalmefene is not expected to change clinical practice for these patients, as shown in Figure A4. However, it is conceivable that, in practice, some physicians—having exhausted all other available management options—might choose to prescribe nalmefene in patients with moderate or severe alcohol dependence who have repeatedly failed to achieve an abstinence goal.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

In England, the lack of referrals to specialist treatment has been associated with perceived difficulties in access to treatment (e.g., waiting lists) and patient preference not to engage in the specialist treatment currently offered (Drummond et al., 2005). There is a general lack of access to specialist

treatment, with only approximately 1 in 18 patients (5.6% [63,000 patients]) receiving alcohol specialist treatment per annum in England (Drummond et al., 2005). Only 13% of the population with alcohol dependence has been identified, yet the majority of these patients do not receive any treatment for the reasons outlined above (Drummond et al., 2005).

There is an unmet need in the management of alcohol dependence, in particular for options that are more easily accessible, that encourage and motivate adherence, and that result in better treatment outcomes (Drummond et al., 2009; EMA, 2010). Currently, psychosocial intervention, such as extended brief intervention or motivational interviewing, is the mainstay of treatment for alcohol-dependent patients with a treatment goal of alcohol reduction (NICE, 2011a). Approximately half of the patients seeking help at a range of services across the United Kingdom were found to choose reduction of alcohol consumption rather than abstinence as their preferred treatment goal when asked (Heather et al., 2010). There is also evidence that achieving a successful outcome of abstinence or reduction is related to initial goal preference, and allowing patients to set their own treatment goal is associated with a higher chance of success, regardless of preference (Adamson et al., 2010; Orford and Keddie, 1986).

A “brief intervention” is the mainstay of treatment in primary care and is the most commonly applied form of psychosocial intervention, if any takes place at all (Expert opinion, Data on File, 2014; Lundbeck survey, Data on File, 2014).

Where it is offered in primary care, this brief intervention usually consists of assessment, information, and brief advice given by the GP or practice nurse to cut down or abstain from drinking. In some areas, but not all, the brief intervention is supplemented by a variety of low-intensity offerings, including psychosocial support of an unspecified nature, group therapy, a physical health check and/or vitamin supplementation. (Expert opinion, Data on File, 2014; Lundbeck survey, Data on File, 2014).

Even in the specialist centres, brief intervention and extended brief intervention are routinely offered for 80%-100% of patients (Lundbeck survey, Data on File, 2014). In secondary care services, substance misuse team workers are unlikely to have any formal training in, or access to, cognitive-behavioural therapy (CBT), behavioural therapies (BT), motivation-enhancement therapy (MET), or social network/environment–based therapy. Secondary services for alcohol problems are very variable across England and Wales and are often provided by trained volunteers whose knowledge and experience may be limited. In reality, the provision of formal CBT, BT, MET, or social network/environment–based therapies by trained therapists (as usually is the case when a clinical study is undertaken) is only likely to take place within small, specialised units often linked to universities or research departments (Expert opinion, Data on File, 2014).

2.7 Please identify the main comparator(s) and justify their selection.

In line with the scope for this technology appraisal, the potential comparators for nalmefene (in conjunction with psychosocial support) are psychological intervention alone and naltrexone (in conjunction with psychosocial support).

The terms “psychosocial support,” “psychosocial intervention,” and “psychological intervention” encompass a variety of different interventions and are often used interchangeably.

Relapse prevention and harm reduction studies

With the development of compounds to treat alcohol dependence, two types of clinical trials have been designed and are proposed by the EMA to assess the effect of these treatments (EMA, 2009): relapse prevention studies and harm reduction studies. Relapse prevention trials are based on an abstinence-oriented approach. In order to assess the efficacy of treatments in these trials, patients should be abstinent or fully detoxified at the time of enrolment or inclusion in the study. The treatment goal is to maintain stable abstinence by prevention of relapse after withdrawal from alcohol/ detoxification. Continued abstinence (after detoxification or the grace period) at the end of the active treatment period and continued abstinence until the end of the study are the primary outcomes assessed.

Harm reduction studies, on the other hand, are based on reduction of alcohol consumption with the aim of assessing the reduction in risk of harmful consequences associated with alcohol use.

This approach provides an alternative to zero-tolerance approaches by incorporating drinking goals such as reduced alcohol consumption that are compatible with the needs of the individual and promote access to services by offering low threshold alternatives to traditional alcohol prevention and treatment (Marlatt, 2002). A clinically significant reduced alcohol intake with subsequent harm reduction is the ultimate treatment goal of these studies. The primary efficacy outcomes assessed in these studies, as recommended by the EMA, include change from baseline in total alcohol consumption (TAC) in g/day, and reduction in heavy drinking days (HDDs), defined as consumption in 1 day of more than 60 g of pure alcohol in men and 40 g in women (EMA, 2009).

NICE CG115 recommends a treatment goal of either abstinence or reduction of alcohol consumption, depending on the severity of alcohol dependence (NICE, 2011a). The NICE guideline recognises that a treatment goal of alcohol reduction has clinical value for some dependent patients and may serve as an intermediate goal towards future abstinence (NICE, 2011a). Based on published literature, the NICE clinical guideline recommends psychosocial interventions as the preferred treatment option in alcohol-dependent patients for whom reduction of alcohol consumption is a medically relevant treatment approach and who do not require detoxification (NICE, 2011a). In addition, due to the limited literature available for this population, the NICE clinical guideline makes an unlicensed recommendation for

naltrexone and acamprosate (in conjunction with psychosocial support) for the reduction of alcohol consumption only for patients for whom psychological intervention alone has failed (NICE, 2011a).

Comparator 1: Psychological/psychosocial intervention

Currently, psychosocial intervention, such as extended brief intervention or motivational interviewing, is the mainstay of treatment for alcohol-dependent patients with a treatment goal of alcohol reduction (NICE, 2011a). NICE recommends psychological interventions (also termed psychosocial interventions or psychosocial support) as the preferred treatment option in alcohol-dependent patients for whom reduction of alcohol consumption is a medically relevant treatment approach and who do not require immediate detoxification (NICE, 2011a).

A psychosocial intervention, in the form of BRENDA, was provided to all treatment groups in the three nalmefene RCTs, and the efficacy results in the licensed population are presented below. It is a requirement of the nalmefene licence that all patients be offered psychosocial support of some description (Nalmefene SPC, 2013).

Comparator 2: Naltrexone (in conjunction with psychosocial support)

Naltrexone is available in England and Wales for the treatment of alcohol dependence and is indicated as adjunctive to psychosocial therapy, with relapse prevention being the treatment goal, and is usually prescribed to patients with moderate or severe alcohol dependence who have reached abstinence following an alcohol withdrawal or detoxification process (NICE, 2011a). Unlike naltrexone, nalmefene is not indicated for patients with moderate and severe alcohol dependence who require immediate detoxification and is not indicated to maintain abstinence.

NICE CG115 makes an unlicensed recommendation for naltrexone and acamprosate in conjunction with psychological interventions for the reduction of alcohol consumption for patients for whom psychological intervention alone as failed (NICE, 2011a).

Lundbeck conducted a systematic literature review to assess the efficacy of naltrexone when used in the same context of care as nalmefene (i.e., in the reduction of alcohol consumption) (see Section 6.7). Similar to the review conducted by NICE (NICE, 2011a), the Lundbeck review found limited evidence assessing naltrexone with psychosocial support in the reduction of alcohol consumption in alcohol-dependent patients, and a conclusion could not be drawn regarding the efficacy of naltrexone with psychosocial support in this patient group. Furthermore, due to the differences in study design, inclusion/exclusion criteria, study objective, and endpoints, as well as a lack of reporting of data from the naltrexone studies, it was not possible to perform an indirect comparison of naltrexone versus nalmefene, which fulfilled the requirements of good practice for evidence synthesis required by NICE (NICE, 2011b).

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

No specific medications need to be used to manage adverse drug reactions.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The nalmefene product label states that nalmefene should only be prescribed in conjunction with continuous psychosocial support focussed on treatment adherence and reducing alcohol consumption. In the nalmefene clinical trial programme, this psychosocial support was delivered in the form of BRENDA. BRENDA, a motivational and adherence-enhancing intervention, emphasises the importance of adherence to treatment by providing positive feedback and help in solving difficulties with adherence. BRENDA was administered to all the patients throughout the treatment period in all three studies, in accordance with the EMA Guideline on alcohol dependence, which states that standardised psychosocial interventions should be allowed in alcohol dependence studies and kept to a constant and low level for all patients (EMA 2010). So besides the cost of nalmefene itself the main resource use associated with nalmefene to the NHS will be the cost of BRENDA. However, none of the BRENDA components are specific to any one illness (Starosta et al., 2006) and constitute what is likely already performed by GPs and specialists when treating patients for alcohol dependence. BRENDA is one of several forms of psychosocial support that can be given with nalmefene; in routine clinical practice, BRENDA can be replaced by any psychosocial support focused on treatment adherence and reducing alcohol consumption.

In UK clinical practice currently, psychosocial intervention – such as extended brief intervention or motivational interviewing – is the mainstay of treatment for alcohol dependent patients with a treatment goal of alcohol reduction irrespective of care setting (Expert opinion, Lundbeck Data on File, 2014). Although there are some differences in the terminology and types of approaches used, these interventions all have a strong focus on motivational interviewing techniques. Practitioners have referred to using these interchangeably; the frequency, duration, and delivery style (group, individual, etc.) of the intervention being the main points of differentiation.

2.10 Does the technology require additional infrastructure to be put in place?

In common with the other pharmacological agents used in the management of alcohol dependence, the nalmefene SPC requires that nalmefene is prescribed in conjunction with continuous psychosocial support. As described in Section 2.9 above, nalmefene can be given in conjunction with any psychosocial support focused on treatment adherence and reducing alcohol consumption. This support should already be in place and available as a consequence of the recommendations set out in NICE CG115.

As noted in Section 1.14, continuous psychosocial support should be considered part of a standard clinical interaction and not a significant change from what would be delivered in common practice (Volpicelli et al., 2001; Johnson et al., 2003; Pettinati et al., 2004; Pettinati et al., 2005; Starosta et al., 2006). Initial interactions may take more time as a treatment alliance is built between the patient and his or her healthcare professional and as issues are raised for the first time. While ongoing interactions are likely to be shorter as a result of the frequent visits and relation build-up, they should include the following elements:

- Monitoring alcohol consumption
- Monitoring medication adherence
- Assessing overall progress
- Providing feedback and support
- Reviewing treatment goals

The components of continuous psychosocial support can be delivered by primary care practitioners with appropriate knowledge in the treatment of alcohol dependence during a routine consultation, with support from local community-based non-statutory alcohol services (Rome, 2014a). Continuous psychosocial support is a simple intervention and is very similar to what is commonly used in routine clinical practice for the management of long-term or chronic conditions. In these circumstances, healthcare providers address a wide variety of behavioural problems in their patients and routinely manage chronic diseases with a combination of clinical advice (that is, feedback together with expressing caring, encouraging progress, providing a positive reinforcement attitude, and educating the patient on the disease) and medication management. Thus, the psychosocial support recommended with the use of nalmefene in the SPC can be delivered during a usual medical consultation in primary care/tier 2 and/or in tier 3 services.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

i. could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

ii. could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g., by making it more difficult in practice for a specific group to access the technology

iii. could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

No equity issues have been identified.

3.1.2 How has the analysis addressed these issues?

Not applicable

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a “step-change” in the management of the condition.

Nalmefene is the first pharmacological treatment licensed in Europe for the reduction of alcohol consumption in alcohol-dependent patients in conjunction with psychosocial intervention focused on treatment adherence and reducing alcohol consumption.

Nalmefene expands treatment options and addresses an unmet medical need for patients who do not require immediate detoxification and who would prefer an initial treatment goal of alcohol reduction. Nalmefene does not require specialist initiation and can be used in primary care. Indeed, nalmefene can be initiated by physicians in primary care without any requirement for

additional testing beyond what is usually performed for patients diagnosed with alcohol dependence. Moreover, it is anticipated that an appropriate psychosocial intervention could be offered by physicians or other professionals within the same routine appointment.

Nalmefene is taken as needed. This dosing suits the different drinking patterns of each individual, ensuring only relevant medication intake, and empowers patients to decide when to take their medication. As-needed dosing allows patients with alcohol dependence to manage their own treatment to stay in control of their drinking, thus empowering patients to manage their own illness. It may also encourage alcohol-dependent patients to engage with the treatment programme and provide a better reflection of consumption and drinking pattern. In the nalmefene phase 3 clinical studies, more than 80% of participants in the nalmefene group adhered to the as-needed dosing regime (Sinclair et al., 2014).

Experience from the nalmefene clinical trials indicates that the availability of a pharmacologic treatment for a person with mild alcohol dependence can improve the way that current need is met. First, it encourages the seeking of medical treatment for people with a stigmatised condition, which contains a denial component as part of the addictive nature of the disease. Second, the assessment step by a healthcare professional (which includes taking a drinking history and offering brief advice on consumption of alcohol during the initial consultation) can have an effect in itself. In the nalmefene phase 3 trials, 35% of patients with a high or very high DRL at baseline reduced their alcohol consumption in the period between the initial visit (screening) and randomisation (Nalmefene SPC, 2013). At randomisation, these patients consumed such a small amount of alcohol that there was little room for further improvement (floor effect) (Nalmefene SPC, 2013).

The totality of the product profile for nalmefene, combined with the fact that there is no requirement for specialist initiation or prescribing, supports secondary prevention outcomes in primary care/tier 2 services for mild alcohol dependence, as well as helps to achieve existing recommendations in both NICE PH24 and NICE CG115 (NICE, 2010a; NICE, 2011a; NICE 2011d).

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life-year (QALY) calculation.

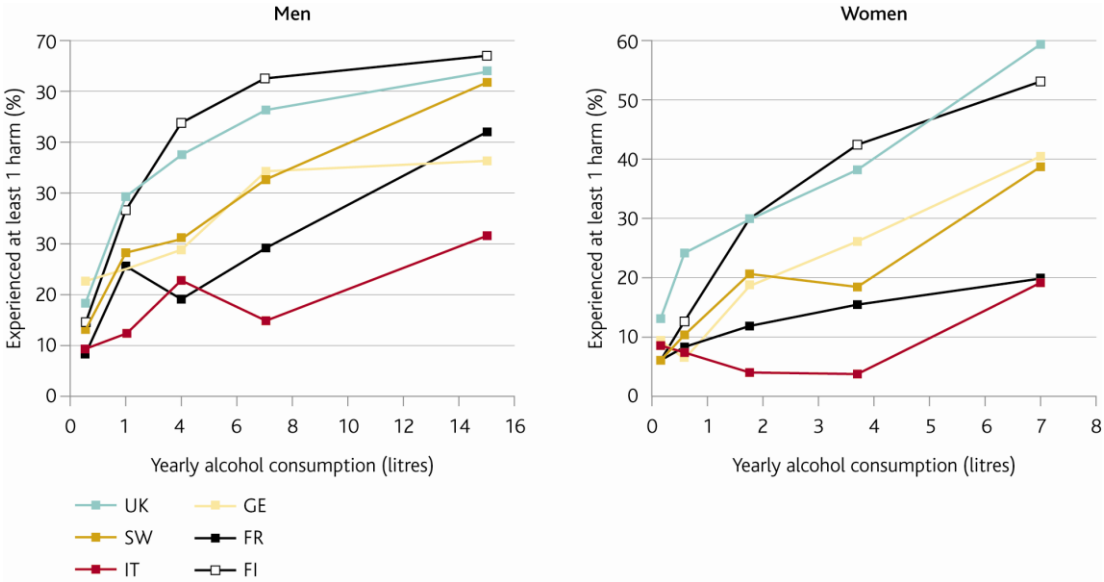
There are many aspects in addition to the prevention of alcohol-attributable illnesses that are positively influenced when reducing alcohol consumption, some of which could be considered as addressing issues of equity. These include improvement in patient’s productivity (employment and absenteeism) (Sheffield University, 2009), improvement in social functioning, reduction in alcohol-related violence, avoidance of accidents, limiting risk of poverty, and reduction in the impact of alcohol problems on family, friends, and society as a whole. Reduction in alcohol consumption is also associated with large savings in the costs of health and social care and of criminal justice services (UK Alcohol Treatment Trial, 2005).

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Alcohol dependence places a large burden on individual health and society and, as described in Section 4.1.2 above, reducing alcohol consumption can have positive outcomes.

In general, the risk of the most commonly experienced negative social consequences of alcohol (e.g., getting into a fight and harming home life, marriage, work, and friendships or social life) increases proportionally with the amount of alcohol consumed (Figure A6) (Norstrom, 2002).

Figure A6. Increasing risk of at least one negative social consequence by yearly alcohol consumption for selected European countries



FI = Finland; FR = France; GE = Germany; IT = Italy; SW = Sweden; UK = United Kingdom.

Source: Norstrom, 2002.

Impact on family

Alcohol dependence can lead to domestic violence, which can result in medical, social, and economic problems. For example, child mistreatment, such as neglect or physical abuse, is higher among individuals reporting heavy drinking, with 25% to 33% of child abuse cases and 50% of child protection cases linked to alcohol (Alcohol Concern UK, 2012). Further information on this aspect is described in the recently-published NICE *Public Health Programme Guidance on Domestic Violence and Abuse—How Services Can Respond Effectively* (PH50) (NICE, 2014).

Impact on wider society

Alcohol dependence can also indirectly affect the wider society, with alcohol being the major contributing factor for road traffic accidents and violent crime. In England and Wales, approximately 50% of all violent assaults are related to alcohol (Anderson et al., 2006; Flatley et al., 2010) (Table A4).

Table A4. Percentage of crime attributable to alcohol consumption in England and Wales

	% linked to alcohol
All crimes	25
Violent crime	48
Robbery	19
Sex offences/rape	58
Source: Anderson et al., 2006	

In addition to its effect on crime, alcohol is responsible for road traffic deaths. In 2007, the number of accidents involving illegal alcohol levels in Great Britain was 14,020 in total, including 410 fatal and 1,760 serious accidents (Institute of Alcohol Studies [IAS], 2009).

Impact on the workplace

Alcohol dependence can also lead to lost working days and affected quality of work (WHO, 2011). For example, in the United Kingdom up to 17 million working days are lost annually due to alcohol-related absenteeism (IAS, 2009). A quarter of accidents in many workplaces involve intoxicated individuals (IAS, 2009). Heavy drinking is associated with decreased work performance and can lead to unemployment, worsening the poverty associated with alcohol dependence (WHO, 2004).

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

Table A5. Decision problem

	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 DRL (≥ 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 DRL without physical withdrawal symptoms, do not require immediate detoxification, and continue to have a high DRL 2 weeks after initial assessment	N/A
Intervention	Nalmefene + PI	Nalmefene + PI	N/A
Comparator(s)	(i) Psychosocial intervention such as cognitive behavioural therapies, behavioural therapies, or social network and environment-based therapies; (ii) Naltrexone + PI	Psychosocial intervention 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), 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 2.7 and 6.7, it was not possible to conduct an indirect treatment comparison due to lack in reported data in the clinical trials of naltrexone's efficacy in the particular group of patients for which nalmefene

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
			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 (e.g., serum ASAT/GGT activities); hospitalisations; controlled drinking, change in number of HDDs, 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 HDDs, 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 technologies being compared. Costs 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	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 mortality.	N/A

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	of alcohol).		
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; ASAT = aspartate aminotransferase; CDT = carbohydrate-deficient transferrin; DRL = drinking risk level; GGT = gamma-glutamyl transferase; HDD = heavy drinking day; MCV = mean corpuscular volume; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PI = psychosocial intervention; TAC = total alcohol consumption.

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the "reference case" (see the NICE document "Guide to the methods of technology appraisal" – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in "Guide to the methods of technology appraisal"**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL = health-related quality of life; NHS = National Health Service; PSS = Personal Social Services; QALY = quality-adjusted life-year.

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's "Guide to the methods of technology appraisal," Sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.2, Appendix 2.

Two systematic reviews to retrieve clinical data were conducted specifically for this submission:

- One systematic review was performed to identify studies evaluating the pharmacological agents nalmefene and naltrexone for reduction of alcohol consumption in actively drinking alcohol-dependent patients. The objectives of this review were to (1) identify studies of nalmefene relevant for this submission, and (2) identify the available evidence on naltrexone when used in the same context as nalmefene (alcohol reduction).

- A second systematic review was conducted to identify clinical trials investigating psychosocial interventions used in alcohol dependence. The purpose of this review was to provide an update of the NICE review of psychosocial interventions (NICE, 2011a), with a focus on interventions specifically listed in the scope for nalmefene, in addition to interventions listed in NICE CG115 that were most similar to BRENDA, the psychosocial treatment used in the nalmefene studies. The following psychosocial interventions were included:

  - Cognitive behavioural therapies
  - Behavioural therapies
  - Social network and environment therapies
  - Brief interventions
  - Motivational enhancement therapy

Sections 6.1.1 and 6.2.1 present the methodology of the systematic review of nalmefene and naltrexone.

The nalmefene studies identified in the systematic review for the pharmacological agents (nalmefene and naltrexone) are described in Sections 6.2.2 to 6.5 and Section 6.9.

Section 6.7 presents the naltrexone studies identified in the systematic review for pharmacological agents, as well as the systematic review for psychosocial interventions.

Systematic review of pharmacological agents

MEDLINE (via PubMed platform), EMBASE (via Dialog platform), Cochrane Library, and PsycINFO databases were searched to identify English-language studies. No date limit was placed on the searches. The searches were

conducted using a combination of search terms and keywords for alcoholism, treatments of interest, and terms related to the study design (e.g., randomised controlled trial [RCT]). The full search strategy is presented in Section **Error! Reference source not found.**.

Clinical trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform Search Portal, International Standard Randomised Controlled Trial Number [ISRCTN] Register) were searched for relevant studies. Bibliographies of systematic review articles were examined to obtain additional relevant references. Bibliographies of accepted studies were also reviewed to identify other potentially relevant references.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table B1 presents the PICOS (population/patients, intervention, comparison, outcomes, study design) inclusion and exclusion criteria used to assess titles and abstracts for the systematic review at screening level 1. Both nalmefene and naltrexone studies were included at screening level 1.

Table B2 presents criteria for level 2 screening of full-text articles, focusing on nalmefene studies only. The level 2 criteria for naltrexone studies are presented in Section 6.7.

Table B1. Eligibility criteria used in the search strategy, level 1 screening for selection of nalmefene and naltrexone studies

	Inclusion criteria	**Exclusion criteria**
Population	• Adults (≥ 18 years) with alcohol dependency	• Children (aged < 18 years)
Interventions	• Treatment with any of the following pharmacological interventions: − Nalmefene − Naltrexone	• None specified
Outcomes	• None specified	• None specified
Study design	• Parallel-group, randomised controlled prospective clinical trials (triple/double/single-blind or open label) • Cross-over, randomised controlled prospective clinical trials (triple/double/single-blind or open label) • Non–randomised controlled clinical trials • Long-term follow-up studies (e.g., open-label follow-up of	• Preclinical studies • Phase 1 studies • Noncomparative phase 2 trials • Prognostic studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Nonsystematic reviews • Genetic studies

	Inclusion criteria	Exclusion criteria
	randomised clinical trials) • Prospective cohort studies and longitudinal studies • Retrospective cohort studies and longitudinal studies • Case-control studies • Cross-sectional studies • Systematic reviews and meta-analyses	

Table B2. Eligibility criteria used in the search strategy, level 2 screening for selection of nalmefene studies

		Exclusion criteria
Population	• Criteria in Table B1	• Criteria in Table B1 • Patients who are abstinent for a prespecified period for randomisation in the study • Patients with a comorbid disorder in addition to the diagnosis of alcohol dependence (e.g., schizophrenia or bipolar disorder) • Patients with coaddiction along with alcohol dependency (e.g., cocaine codependence or pathologic gambling)
Interventions	• Treatment with oral nalmefene 20 mg as-needed in conjunction with any type of psychosocial support	• Nalmefene used at a dose other than 20 mg • Nalmefene not used as-needed
Comparator	• Nalmefene in conjunction with any type of psychosocial support • Placebo in conjunction with any type of psychosocial support or best supportive care	• None specified
Outcomes[a]	• Studies reporting endpoints of level and/or pattern of alcohol consumption	• None specified
Study design	• Criteria in Table B1 • Randomised controlled trials	• Studies that had a detoxification or alcohol-withdrawal process period before randomisation • Studies only reported as abstract/poster

[a] 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 article shows that the patients were actively drinking at baseline.

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the

statement should equal the total number of studies listed in Section 6.2.4.

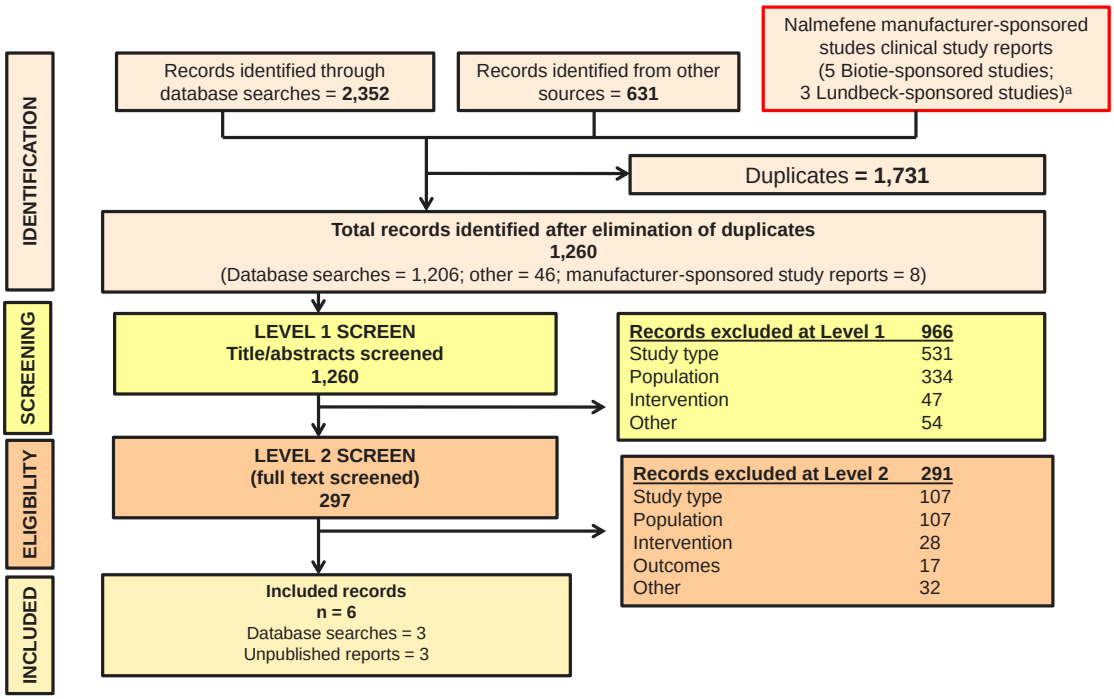
Figure B1 describes the study attrition results for quantitative analysis in a PRISMA-style diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Note that the same level 1 screening process was used for nalmefene and naltrexone studies (Figure B1). The PRISMA diagram presented in Figure B1 presents results for the level 2 review process focussing on nalmefene studies. Section 6.7 describes results for the level 2 review process focusing on naltrexone studies; the PRISMA diagram relevant to the level 2 review of naltrexone studies is also presented in Section 6.7.

The literature search yielded 1,260 relevant citations, once duplicates between databases and Internet sources were removed. A total of 966 records were excluded at level 1 screening of titles/abstracts, and a further 291 articles were excluded at the level 2 full-text article screening stage, particularly because of nonrelevant study type (n = 107) or nonrelevant population (n = 107). After applying the level 1 and level 2 screening criteria, six records describing three studies (ESENSE1, ESENSE2 and SENSE) evaluating nalmefene in alcohol dependence were included and extracted. The six records were Mann et al., 2013 (ESENSE1 primary manuscript), Gual et al., 2013 (ESENSE2 primary manuscript), van den Brink et al., 2013 (which describes the licensed population from ESENSE1 and 2, both as individual studies and pooled), and Lundbeck clinical study reports for ESENSE1, ESENSE2 and SENSE.

All five Biotie-sponsored studies (2 published and 3 unpublished) were excluded from the review at the level 2 screen. Reasons for excluding these studies are outlined in Section **Error! Reference source not found.**, Appendix 2: the main reasons for exclusion were study population, use of nalmefene outside its indication, and study design.Thus, all five Biotie-sponsored studies were considered irrelevant to the systematic review and the scope of a health technology assessment submission for nalmefene in accordance with the product label and the decision problem.

Figure B1. Flow diagram of identification process for systematic review of nalmefene studies



[a] These nalmefene manufacturer-sponsored clinical study reports (5 Biotie-sponsored studies [including 3 unpublished studies] and 3 Lundbeck-sponsored studies [including one unpublished study [SENSE]) were added separately. These were all screened against the same eligibility criteria as in Table B1 and Table B2 to determine whether they were relevant to the decision problem in this submission.

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The primary publication for the ESENSE1 study is Mann et al. (2013), and the primary publication for the ESENSE2 is Gual et al. (2013). These publications provide full descriptions of the respective studies and present results for the total study population.

One article (van den Brink et al., 2013) provides results for ESENSE1 and ESENSE2 separately, and also presents pooled analysis of the licensed population from these two studies.

The Lundbeck internal clinical study reports for ESENSE 1 (Lundbeck, 2012b) and ESENSE 2 (Lundbeck, 2012c) have also been used to provide additional key data that have not been published and are therefore not available in the public domain.

The data source for the SENSE study is the Lundbeck internal clinical study report (Lundbeck, 2012a). SENSE is due to be published in Q2 2014.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table B3 presents details of the three relevant RCTs of nalmefene in patients with alcohol dependence: ESENSE1 (Mann et al., 2013; Lundbeck, 2012b), ESENSE2 (Gual et al., 2013; Lundbeck, 2012c), and SENSE (Lundbeck, 2012a).

Only trials assessing nalmefene + PI versus placebo + PI were identified in the systematic review: no trials assessing nalmefene versus naltrexone were identified.

Table B3. List of relevant RCTs

Trial acronym	Intervention	Comparator	Population	Primary study reference; trial number
ESENSE1	18 mg nalmefene taken as needed for 6 months	Placebo taken as needed for 6 months	Patients with alcohol dependence	Mann et al., 2013; Lundbeck, 2012b
ESENSE2	18 mg nalmefene taken as needed for 6 months	Placebo taken as needed for 6 months	Patients with alcohol dependence	Gual et al., 2013; Lundbeck, 2012c
SENSE	18 mg nalmefene taken as needed for 52 weeks	Placebo taken as needed for 52 weeks	Patients with alcohol dependence	Lundbeck, 2012a

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

ESENSE1, ESENSE2, and SENSE all compared nalmefene + PI (BRENDA) with placebo + PI in patients with alcohol dependence.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Three RCTs were identified, which described three studies, ESENSE1, ESENSE2, and SENSE. Section 6.2.3 describes the data sources used: these three studies are discussed in full in this submission.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in Section 6.8 and key details should be presented in a table; the following is a suggested format.

No non-RCTs were considered relevant to the decision problem.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

ESENSE1 and ESENSE2 were 6-month efficacy studies designed to evaluate the effect of as-needed use of nalmefene on alcohol consumption in patients with alcohol dependence during a treatment period of 24 weeks. SENSE was a 52-week study to evaluate the long-term safety and tolerability of as-needed nalmefene with a protocol amendment after study initiation to include efficacy analyses at month 6. SENSE was a predefined safety study with no power calculations undertaken on efficacy outcomes prior to the commencement of the study and a trial design that reflected a primary safety study (3:1 randomisation). All three studies assessed as-needed use of nalmefene in patients with alcohol dependence, diagnosed according to DSM-IV criteria.

The three studies were conducted in Europe and randomised 1,997 patients with alcohol dependence to nalmefene + PI or placebo + PI. Psychosocial intervention, in the form of BRENDA, was provided to all treatment groups in the three studies.

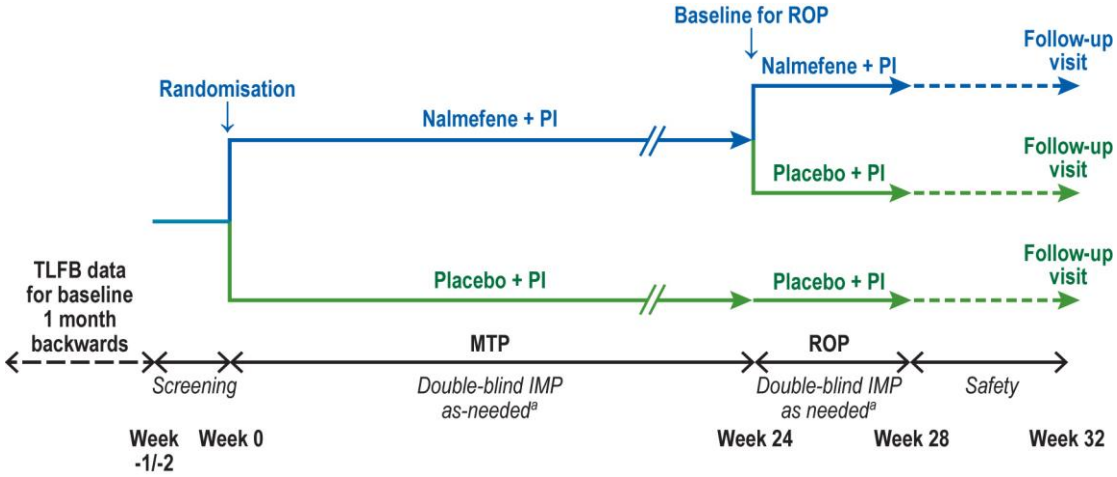
The BRENDA approach has six components: (1) a biopsychosocial evaluation, (2) a report of findings from the evaluation given to the patient, (3) empathy, (4) addressing patient needs, (5) providing direct advice, and (6) assessing patient reaction to advice and adjusting the treatment plan as needed. BRENDA was developed for use in combination with addiction pharmacotherapy to enhance medication adherence, but none of the BRENDA components are specific to any one illness (Starosta et al., 2006).

BRENDA emphasises the importance of adherence to treatment by providing positive feedback and help in solving difficulties with adherence; it formalises the interaction with the patient and outlines a strategy of therapeutic care that is comprehensive but also focuses on the individual patient's medical and psychological needs.

In the three nalmefene studies, BRENDA was administered, using the accompanying manual, by trained site personnel (e.g., investigators, nurses, and psychologists) who were instructed to limit the sessions to approximately 15 to 30 minutes (except for the first session administered at randomisation, which was approximately 30 to 40 minutes). No other psychosocial support was allowed during the studies. BRENDA was administered to standardise the medical advice and support given to patients across different sites and countries. Patients were not required to achieve abstinence prior to entering the study, nor at any point during the study.

The two 6-month efficacy studies, ESENSE1 and ESENSE2, were identical in design; both studies began with a 1- to 2-week screening period, after which patients were randomised 1:1 to 24 weeks of as-needed treatment with nalmefene + BRENDA or placebo + BRENDA (Figure B2). The patients who completed 24 weeks of double-blind treatment entered a 4-week, double-blind run-out period (ROP). The patients randomised to nalmefene were rerandomised 1:1 to receive nalmefene or placebo, and the patients randomised to placebo continued on placebo (rerandomisation was done concurrently with the initial randomisation). A safety follow-up visit was scheduled for 4 weeks after completion of the ROP or after withdrawal from the study.

Figure B2. Schematic overview of the study design of ESENSE1 and ESENSE2



IMP = investigational medicinal product; MTP = main treatment period; PI = psychosocial intervention; ROP = run-out period; TLFB = timeline follow-back.

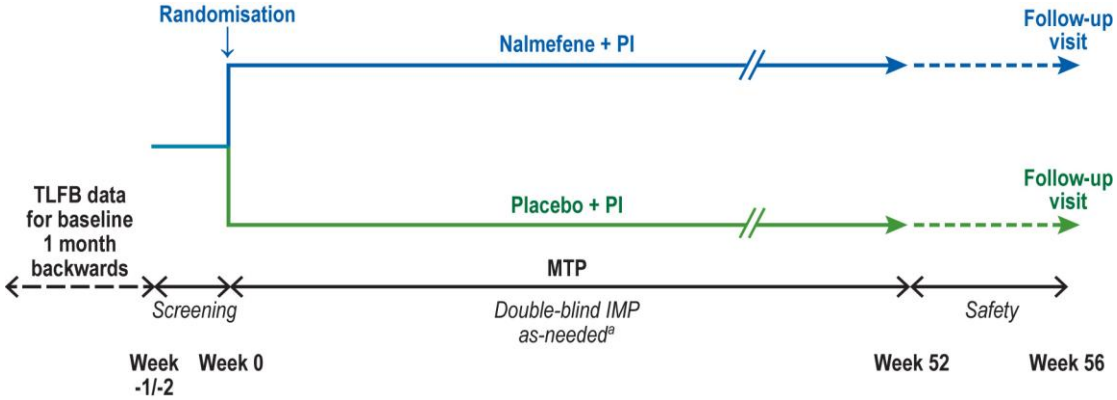
[a] ESENSE1 (n = 604); ESENSE2 (n = 718).

Note: BRENDA was provided at weeks 0, 1, 2, 4, 8, 12, 16, 20, 24, and 28.

Source: Lundbeck, 2012e.

Similar to the ESENSE studies, the 52-week safety study (SENSE) also commenced with a 1- to 2-week screening period, after which patients were randomised 3:1 to 52 weeks of as-needed treatment with nalmefene + BRENDA or placebo + BRENDA (Figure B3). A safety follow-up visit was scheduled for 4 weeks after completion of the study or after withdrawal from the study.

Figure B3. Schematic overview of the study design of SENSE



IMP = investigational medicinal product; PI = psychosocial intervention; TLFB = timeline follow-back.

[a] n = 675 (3:1; nalmefene:placebo); BRENDA was provided at weeks 0, 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.

Source: Lundbeck, 2012e.

The timeline follow-back (TLFB) method was used to assess self-reported alcohol consumption. The TLFB provides information on an individual's pattern, variability, and amount of drinking, and its use is recommended in the EMA guideline on the development of medicinal products for the treatment of alcohol dependence (EMA, 2010). The method has been widely used in clinical studies in alcohol dependence and has shown to give reliable retrospective self-reports of drinking in outpatient populations (Maisto et al., 1979). All alcohol drinking variables used in the studies were derived from the TLFB data, and baseline drinking levels were obtained from TLFB data from the 4 weeks preceding the screening visit.

Table B4 presents the methodology of the ESENSE1, ESENSE2, and SENSE phase 3 trials.

Table B4. Comparative summary of methodology of ESENSE1, ESENSE2, and SENSE

Trial no. (acronym)	Study 12014A (ESENSE1)	Study 12023A (ESENSE2)	Study 12013A (SENSE)
Location (number of sites)	Austria (4), Finland (11), Germany (16), and Sweden (8)	Belgium (7), Czech Republic (3), France (16), Italy (10), Poland (7), Portugal (4), and Spain (10)	Czech Republic (5), Estonia (5), Hungary (2), Latvia (4), Lithuania (2), Poland (15), Russia (8), Slovakia (4), Ukraine (10), and the UK (5)
Design	Multinational, multisite, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose, as-needed dosing (18 mg nalmefene)	Multinational, multisite, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose, as-needed dosing (18 mg nalmefene)	Multinational, multisite, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose, as-needed dosing (18 mg nalmefene)
Duration of study	24-week study	24-week study	52-week study
Method of randomisation	Block randomisation using a computer-generated list. At each site, the 4-digit randomisation number was to be assigned consecutively, starting with the lowest number available.	Block randomisation using a computer-generated list. At each site, the 4-digit randomisation number was to be assigned consecutively, starting with the lowest number available.	Block randomisation using a computer-generated list. At each site, the 4-digit randomisation number was to be assigned consecutively, starting with the lowest number available.
Method of blinding (care provider, patient and outcome assessor)	Double-blind study in which nalmefene and placebo tablets were identical in appearance. Group assignment was concealed from investigators and participants. Two sets of opaque, sealed envelopes containing the randomisation code for each patient were kept by Global Pharmacovigilance, Lundbeck, and the investigator or pharmacist. The code could be broken in case of emergency.	Double-blind study in which nalmefene and placebo tablets were identical in appearance. Group assignment was concealed from investigators and participants. Two sets of opaque, sealed envelopes containing the randomisation code for each patient were kept by Global Pharmacovigilance, Lundbeck, and the investigator or pharmacist. The code could be broken in case of emergency.	Double-blind study in which nalmefene and placebo tablets were identical in appearance. Group assignment was concealed from investigators and participants. Two sets of opaque, sealed envelopes containing the randomisation code for each patient were kept by Global Pharmacovigilance, Lundbeck, and the investigator or pharmacist. The code could be broken in case of emergency.
Intervention(s) (n =) and comparator(s) (n =)	Nalmefene + PI (n = 306) Placebo + PI (n = 298)	Nalmefene + PI (n = 358) Placebo + PI (n = 360)	Nalmefene + PI (n = 509) Placebo + PI (n = 166)
Primary outcomes (including scoring methods and timings of assessments)	See Table B8 in Section 6.3.5.	See Table B8 in Section 6.3.5.	See Table B8 in Section 6.3.5.

Trial no. (acronym)	Study 12014A (ESENSE1)	Study 12023A (ESENSE2)	Study 12013A (SENSE)
Secondary outcomes (including scoring methods and timings of assessments)	See Table B8 in Section 6.3.5.	See Table B8 in Section 6.3.5.	See Table B8 in Section 6.3.5.
Duration of follow-up	4-week safety follow-up	4-week safety follow-up	4-week safety follow-up
PI = psychosocial intervention. Sources: EMA, 2012; Gual et al., 2013; Lundbeck, 2012a; Mann et al., 2013; van den Brink et al., 2012.			

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Patients in the ESENSE1, ESENSE2, and SENSE trials were recruited from outpatient clinics, from the study sites' own patient pools, by referrals to the study sites, or by using advertisements. Table B5 presents eligibility criteria for the three studies.

Table B5. Eligibility criteria in the ESENSE1, ESENSE2, and SENSE trials

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
ESENSE1	• Aged ≥ 18 years • Inpatients and outpatients with a primary diagnosis of alcohol dependence according to DSM-IV-TR • ≥ 6 HDDs in the 4 weeks preceding the screening visit • ≤ 14 abstinent days in the 4 weeks preceding the screening visit • Average alcohol consumption at medium risk level or above in the 4 weeks preceding the screening visit	• Withdrawal symptoms requiring medication (CIWA-Ar, Revised, score ≥ 10) • History of delirium tremens or alcohol withdrawal seizures • Cognitive impairment that was likely to interfere with the patient's understanding of the study and its procedures • An ASAT or ALAT value > 3 times the upper limit of the reference range, or a laboratory value outside the reference range (based on samples taken at the screening visit) that was clinically significant, as judged by the investigator • Clinically significant abnormal vital signs or ECG
ESENSE2	• As in ESENSE1	• As in ESENSE1
SENSE	• Aged ≥ 18 years • Outpatients with a primary diagnosis of alcohol dependence according to DSM-IV-TR • ≥ 6 HDDs in the 4 weeks preceding the screening visit • ≤ 14 abstinent days in the 4 weeks preceding the screening visit • Average alcohol consumption at low risk level or above in the 4 weeks preceding the screening visit	• Withdrawal symptoms requiring medication (CIWA-Ar, Revised, score ≥ 10) • History of delirium tremens or alcohol withdrawal seizures • Cognitive impairment that was likely to interfere with the patient's understanding of the study and its procedures • An ASAT or ALAT value > 3 times the upper limit of the reference range, or a laboratory value outside the reference range (based on samples taken at the screening visit) that was clinically significant, as judged by the investigator • Clinically significant abnormal vital signs or ECG

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; CIWA-Ar = Clinical Institute Withdrawal Assessment for Alcohol; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; ECG = electrocardiogram; HDD: heavy drinking day. Sources: Gual et al., 2013; Lundbeck, 2012e; Mann et al., 2013.		

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Information on baseline patient characteristics for the total clinical trial population can be found in Section **Error! Reference source not found.**, Appendix 4.

In ESENSE1, ESENSE2, and SENSE, the demographic and baseline characteristics for the patients with a high/very high DRL at baseline and randomisation were similar to those for the corresponding total clinical trial population, except for baseline drinking values and baseline Clinical Global Impression-Severity (CGI-S) scores, which were higher in the licensed population.

Table B6 and Table B7 present baseline patient characteristics for the licensed population of patients with a high/very high DRL at baseline and randomisation.

In ESENSE1 and ESENSE2, there were no clinically relevant differences in baseline characteristics between treatment groups (Table B6).

Table B6. Baseline characteristics of patients with a high/very high DRL at baseline and randomisation in ESENSE1 and ESENSE2 (APRS)—licensed population

Baseline characteristic		ESENSE1		ESENSE2	
		Nalmefene + PI	Placebo + PI	Nalmefene + PI	Placebo + PI
Number of patients		180	170	155	162
Patient demographics					
Age (years), mean (SD)		50.9 (10.0)	52.9 (8.8)	45.4 (10.3)	44.1 (10.3)
Sex, %		Female: 36.7 Male: 63.3	Female: 38.2 Male: 61.8	Female: 29.7 Male: 70.3	Female: 31.5 Male: 68.5
Race, n (%)	White	180 (100)	170 (100)	153 (98.7)	159 (98.1)
	Black	—	—	2 (1.3)	2 (1.2)
	Asian	—	—	—	1 (0.6)
	Other	—	—	—	—
Body mass index, mean		26.7 (4.6)	26.9 (4.2)	25.1 (4.9)	25.3 (4.3)

Baseline characteristic		ESENSE1		ESENSE2	
		Nalmefene + PI	Placebo + PI	Nalmefene + PI	Placebo + PI
Living arrangement, n (%)	Alone	[redacted]	[redacted]	[redacted]	[redacted]
	Single with children	[redacted]	[redacted]	[redacted]	[redacted]
	With spouse or partner	[redacted]	[redacted]	[redacted]	[redacted]
	With spouse or partner and children	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]
Education, n (%)	Not known	[redacted]	[redacted]	[redacted]	[redacted]
	Other general/ practical education	[redacted]	[redacted]	[redacted]	[redacted]
	Primary education or less	[redacted]	[redacted]	[redacted]	[redacted]
	Secondary education/ high school	[redacted]	[redacted]	[redacted]	[redacted]
	Tertiary/ further education or university	[redacted]	[redacted]	[redacted]	[redacted]
Alcohol history					
Number of HDDs in 4 weeks, mean (SD)		23.0 (5.9)	23.1 (5.5)	22.7 (9)	21.6 (6.4)
TAC (g/day), mean (SD)		102 (42.9)	98.6 (40.5)	114 (47.8)	108 (47.9)
CGI-S, mean (SD)		4.1 (1.4)	4.2 (1.4)	4.4 (1.3)	4.3 (1.4)
DRL (%)	Low	[redacted]	[redacted]	[redacted]	[redacted]
	Medium	[redacted]	[redacted]	[redacted]	[redacted]
	High	[redacted]	[redacted]	[redacted]	[redacted]
	Very High	[redacted]	[redacted]	[redacted]	[redacted]
DrInC-2R total score, mean (SD)		35.0 (18.1)	35.3 (17.7)	48.3 (24.5)	49.5 (24.0)
ADS total score, mean (SD)		12.7 (5.6)	11.8 (4.8)	15.4 (6.1)	14.9 (6.1)
Age at first drinking experience (years), mean (SD)		[redacted]	[redacted]	[redacted]	[redacted]
Age at onset of drinking problem (years), mean (SD)		37.9 (13.3)	38.4 (12.1)	32.8 (10.5)	31.6 (9.9)
Alcohol family history, n (%)		112 (62.2)	117 (68.8)	99 (63.9)	92 (56.8)
Treated for alcohol dependence previously, n (%)		46 (25.6)	45 (26.5)	59 (38.1)	67 (41.4)
Treated for alcohol withdrawal previously, n (%)		[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristic		ESENSE1		ESENSE2	
		Nalmefene + PI	Placebo + PI	Nalmefene + PI	Placebo + PI
Treated for alcohol dependence/withdrawal previously, n (%)		59 (32.8)	63 (37.1)	64 (41.3)	75 (46.3)
Smoking habits, n (%)	Current	[redacted]	[redacted]	[redacted]	[redacted]
	Never	[redacted]	[redacted]	[redacted]	[redacted]
	Occasional	[redacted]	[redacted]	[redacted]	[redacted]
	Past	[redacted]	[redacted]	[redacted]	[redacted]
Prior substance abuse, n (%)		[redacted]	[redacted]	[redacted]	[redacted]

ADS = Alcohol Dependence Scale; APRS = all-patients-randomised set; CGI-S = Clinical Global Impression-Severity; DRL = drinking risk level; DrInC-2R = Drinker Inventory of Consequences; HDD = heavy drinking day; PI = psychosocial intervention; SD = standard deviation; TAC = total alcohol consumption.

[redacted]

Source: Lundbeck 2012e

In the SENSE study, the proportion of patients with a family history of alcohol problems was higher in the nalmefene + PI group (50.3%) compared with the placebo + PI group (35.7%) (Table B7). The proportion of patients who had previously been treated for alcohol dependence was lower in the nalmefene + PI group (22.1%) compared with the placebo + PI group (31.0%) (Table B7).

Table B7. Baseline characteristics of patients with a high/very high DRL at baseline and randomisation in the SENSE trial (APRS)—licensed population

Baseline characteristic		SENSE	
		Nalmefene + PI	Placebo + PI
Number of patients		145	42
Age (years), mean (SD)		46.2 (11.7)	46.2 (12.5)
Sex, (%)		Female: 22.1 Male: 77.9	Female: 23.8 Male: 76.2
Race, n (%)	White	145 (100)	42 (100)
	Black	—	—
	Asian	—	—
	Other	—	—
Body mass index (kg/m^2) (SD)		27.2 (4.6)	27.0 (5.1)
Living arrangement, n (%)	Alone	22 (15.2)	8 (19.0)
Number of HDDs in 4 weeks, mean (SD)		19.2 (6.3)	18.6 (6.4)
TAC (g/day), mean (SD)		101 (44.6)	101 (46.9)
CGI-S, mean (SD)		4.0 (1.1)	4.0 (1.2)
DrInC-2R total score, mean (SD)		46.6 (22.7)	47.4 (26.0)
ADS total, mean (SD)		15.5 (6.2)	16.9 (8.0)
Age at onset of drinking problem (years), mean (SD)		35.1 (13.1)	35.2 (13.2)
Alcohol family history, n (%)		73 (50.3)	15 (35.7)

Baseline characteristic		SENSE	
		Nalmefene + PI	Placebo + PI
Treated for alcohol dependence previously, n (%)		32 (22.1)	13 (31.0)
Treated for alcohol withdrawal previously, n (%)		31 (21.4)	10 (23.8)
DRL	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

ADS = Alcohol Dependence Scale; APRS = all-patients randomised set; CGI-S = Clinical Global Impression-Severity; DRL = drinking risk level; DrInC-2R = Drinker Inventory of Consequences; HDD = heavy drinking day; PI = psychosocial intervention; SD = standard deviation; TAC = total alcohol consumption.

[redacted]

Source: Lundbeck 2012e.

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table B8 presents primary and secondary outcomes measured in ESENSE1, ESENSE2, and SENSE.

The efficacy of nalmefene in ESENSE1 and ESENSE2 was measured using two co-primary endpoints: change in the monthly number of HDDs and change in monthly TAC.

The co-primary endpoints of HDD and TAC were in accordance with the recommendations in the EMA guideline on the development of medicinal products for the treatment of alcohol dependence (EMA, 2010). The EMA considers both HDD and TAC as primary variables and emphasises that a clinically relevant difference compared with placebo should be demonstrated (EMA, 2010).

An HDD was defined as a day with a consumption of alcohol ≥ 60 g for men and ≥ 40 g for women. TAC was defined as mean daily alcohol consumption in grams per day over a month (28 days). This was in accordance with the EMA guideline, which states that if a study drug addresses the goal of clinically significant moderation, efficacy should be expressed by a reduction in the number of HDDs and a change from baseline in TAC (EMA, 2010).

In the SENSE study, the primary objective on efficacy and the co-primary endpoints (change from baseline in monthly TAC and HDDs at month 6) were added as an amendment to the protocol while the study was ongoing to strengthen the scientific value of the study. No protocol amendments were made to components originally developed for a study designed to assess the safety and tolerability of nalmefene.

Table B8. Primary and secondary outcomes of ESENSE1, ESENSE2, and SENSE

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
ESENSE1 and ESENSE2	Evaluate the effect of as-needed use of nalmefene on alcohol consumption based on the monthly number of HDDs and monthly TAC in patients with alcohol dependence during a treatment period of 24 weeks	According to the EMA guidelines, if a study drug addresses the goal of clinically significant moderation, efficacy should be expressed by change from baseline in TAC (presented as mean daily alcohol consumption in grams per day over a month) as well as by reduction in the number of HDDs (defined as ≥ 60 g/day of pure alcohol in men and ≥ 40 g/day of pure alcohol in women). The EMA considers both of these outcomes, TAC and HDDs, as primary variables and emphasises that a clinically relevant difference compared with placebo should be demonstrated (EMA, 2010).	Effect of as-needed use of nalmefene during a treatment period of 24 weeks on: • Proportion of responders based on various drinking measures − RSDRL response (key secondary efficacy endpoint) − TAC response (≥ 30%, ≥ 50%, or ≥ 70% reduction [R70] in TAC from baseline; R70 was added as a post hoc analysis) (ESENSE1) − RLDRL response − Number of NDDs − No HDDs (ESENSE2) • Alcohol dependence symptoms and clinical status − CGI-I − CGI-I response (added as a post hoc analysis) − CGI-S − ADS total score − DrInC-2R • Liver function and other clinical safety laboratory tests − GGT − ALAT − MCV − %CDT • Pharmacoeconomic outcomes	The EMA also recommends evaluation of responders as a secondary efficacy endpoint by evaluating the proportion of subjects with a 50%, 70%, and 90% reduction in alcohol consumption. Another option recommended is the evaluation of proportion of patients with a significant categorical shift in WHO risk levels of drinking. The EMA also proposes the use of validated biomarkers (e.g., CDT, MCV, ALAT, GGT) at baseline and follow-up assessments during the course of treatment to monitor the effect of treatment (EMA, 2010). The TLFB method was used for drinking measurements. It provides information on an individual's pattern, variability, and amount of drinking. This method has been widely used in clinical studies in alcohol dependence and has shown to give reliable retrospective self-reports of drinking in outpatients.

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
			– SF-36 subscale scores – EQ-5D and VAS scores – RUMQ-ADP – BMRCQ • Treatment withdrawal effects after 24 weeks of as-needed nalmefene treatment • Safety and tolerability of as-needed use of nalmefene (AEs, clinical safety laboratory tests, vital signs, weight, ECGs, POMS score)	
SENSE	• Evaluate long-term safety and tolerability of as-needed use of nalmefene vs. placebo over a period of 52 weeks in patients with alcohol dependence • Evaluate the effect of as-needed use of nalmefene on alcohol consumption using the monthly number of HDDs and the monthly TAC in patients with alcohol dependence during a treatment period of 24 weeks (co-primary efficacy	As above	Evaluate the effect of as-needed use of nalmefene during a treatment period of 24 weeks on: • Proportion of responders based on various drinking measures – RSDRL response (key secondary efficacy endpoint) – TAC response (≥ 30%, ≥ 50%, or ≥ 70% reduction [R70] in TAC from baseline) – RLDRL response – Number of NDDs • Alcohol dependence symptoms and clinical status – CGI-I – CGI-I response (added as a post hoc analysis) – CGI-S – DrInC-2R • Liver function and other clinical	As above

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
	endpoints)[a]		safety laboratory tests − GGT − ALAT − MCV − %CDT • Pharmacoeconomic outcomes − SF-36 subscale scores − EQ-5D and VAS scores − RUMQ-ADP − BMRCQ • Long-term effect over a period of 52 weeks on: − Reduction of alcohol consumption − Alcohol dependence symptoms and clinical status − Liver function and other biological laboratory tests − Pharmacoeconomic outcomes • Safety and tolerability of as-needed use of nalmefene (AEs, clinical safety laboratory tests, vital signs, weight, ECGs, POMS score)	

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice

[a] Added as co-primary endpoints after a protocol amendment while the study was ongoing to strengthen the scientific value of the study.

ADS = Alcohol Dependence Scale; AE = adverse event; ALAT = alanine aminotransferase; BMRCQ = Brief Measure of Readiness to Change Questionnaire; CDT = carbohydrate-deficient transferrin; CGI-I = Clinical Global Impression-Global Improvement; CGI-S = Clinical Global Impression-Severity; DrInC-2R = Drinker Inventory of Consequences; DRL = drinking risk level; ECG = electrocardiogram; EMA = European Medicines Agency; EQ-5D = EuroQol-5 Dimensions; GGT = gamma-glutamyltransferase; HDD = heavy drinking day; MCV = mean corpuscular volume; NDD = nondrinking days; POMS = Profile of Mood States; R70 = ≥ 70% reduction in TAC; RLDRL = response defined as a downward shift from baseline in DRL to low DRL or lower; RSDRL = response defined as a downward shift from baseline in DRL by two categories; RUMQ-ADP = Resource Use Measurement Questionnaire – Alcohol Dependence; SF-36 = 36-item Short-form Health Survey; TAC = total alcohol consumption; TLFB = timeline follow-back; VAS = visual analogue scale; WHO = World Health Organization.

Sources: Gual et al., 2013; Lundbeck 2012a-c, 2012e; Mann et al., 2013.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B9 presents a summary of the statistical analyses conducted in ESENSE1, ESENSE2, and SENSE.

Table B9. Summary of statistical analyses in ESENSE1, ESENSE2, and SENSE

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ESENSE1	**Primary objective:** • To demonstrate a difference in the treatment effect between placebo and as-needed nalmefene for change from baseline to month 6 in number of HDDs and monthly TAC **Secondary objectives:** • To evaluate the effect of as-needed use of nalmefene in patients with alcohol dependence during a treatment period of 24 weeks on: − Proportion of responders based on various drinking measures − Alcohol dependence symptoms and clinical status − Liver function and other clinical safety laboratory tests − Pharmacoeconomic outcomes • To evaluate treatment withdrawal effects after 24 weeks of as-needed nalmefene treatment • To evaluate the safety and tolerability of as-needed nalmefene in patients with	All efficacy analyses were conducted on the FAS. Both co-primary efficacy variables were analysed using MMRM and OC, with the baseline 1 score as a covariate, and site, sex, time in months (months 1-6), and treatment as fixed effects, with the estimated treatment difference at month 6 tested at the 5% level of significance. The key secondary efficacy analysis of RSDRL at month 6 used LREG, with country, sex, baseline 1 DRL, and treatment as fixed effects, and missing values imputed as nonresponse. Analyses of the co-primary endpoints and of the key secondary endpoint (RSDRL) and the sensitivity analyses for both the co-primary and key secondary endpoints were repeated post hoc for the patients with a high/very high DRL at baseline and randomisation.	A minimum of 600 patients were planned for enrolment based on an expected 35% withdrawal rate at month 6 and assuming a correlation of 0.7 between the co-primary efficacy variables. The sample size calculation was based on a standard deviation for the change from baseline in number of HDDs of 7 days and the change from baseline in TAC of 36.5 g/day. With a significance level of 5%, 300 patients in each treatment group would provide a power of at least 90% for detecting a difference of 3 HDDs and 12 g/day in the TAC.	Sensitivity analyses were conducted for each of the co-primary efficacy variables: an MMRM analysis (in which monthly observations were disregarded if there were < 14 days of data) and ANCOVA by month using OC, LOCF, or BOCF. Post hoc ANCOVA analyses were performed for the co-primary efficacy variables in which missing values were imputed using PMI based on the mean reduction observed at month 1 in the placebo group (adjusted for sex). Additional post hoc analyses were performed to compare the effect of nalmefene vs. placebo in the patients who, at the time of randomisation, still fulfilled the requirements prespecified in the protocol regarding alcohol consumption for the screening visit, using an MMRM model. Post hoc ANCOVA analyses using LOCF were also performed. Sensitivity analyses were performed for the key secondary efficacy endpoint using an LREG analysis (in which monthly observations were disregarded if there were < 14 days of data) and analyses using OC or LOCF. In addition, a post hoc analysis was performed in which missing values were imputed using individual

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	alcohol dependence			patient-predicted values of TAC derived from the MMRM model used in the primary analysis of TAC.
ESENSE2	**Primary objective:** • To demonstrate a difference in the treatment effect between placebo and as-needed nalmefene for change from baseline to month 6 in number of HDDs and monthly TAC **Secondary objectives:** • To evaluate the effect of as-needed use of nalmefene in patients with alcohol dependence during a treatment period of 24 weeks on: − Proportion of responders based on various drinking measures − Alcohol dependence symptoms and clinical status − Liver function and other clinical safety laboratory tests − Pharmacoeconomic outcomes • To evaluate treatment withdrawal effects after 24 weeks of as-needed nalmefene treatment • To evaluate the safety and	All efficacy analyses were conducted on the FAS. Both co-primary efficacy variables were analysed using MMRM and OC, with the baseline 1 score as a covariate, and site, sex, time in months (months 1-6), and treatment as fixed effects, with the estimated treatment difference at month 6 tested at the 5% level of significance. The key secondary efficacy analysis of RSDRL at month 6 used LREG, with country, sex, baseline 1 DRL, and treatment as fixed effects, and missing values were imputed using individual patient-predicted values of TAC from the MMRM model. Analyses of the co-primary endpoints and of the key secondary endpoint (RSDRL) and the sensitivity analyses for both the co-primary and key secondary endpoints were repeated post hoc for the patients with a high/very high DRL at baseline and randomisation.	A minimum of 600 patients were planned for enrolment based on an expected 35% withdrawal rate at month 6 and assuming a correlation of 0.7 between the co-primary efficacy variables. The sample size calculation was based on a standard deviation for the change from baseline in number of HDDs of 7 days and the change from baseline in TAC of 36.5 g/day. With a significance level of 5%, 300 patients in each treatment group would provide a power of at least 90% for detecting a difference of 3 HDDs and 12 g/day in the TAC. The sample size was increased to 700 patients (350 patients in each treatment group) after a blinded review of the data indicated higher than anticipated standard deviations and lower	Sensitivity analyses were performed using an MMRM analysis (in which monthly observations were disregarded for a patient if there were < 14 days with data); ANCOVA by month, using OC, LOCF, BOCF, or PMI; MMRM using MI; and incidence (recurrence) of HDDs. Additional post hoc analyses were performed to compare the effect of nalmefene vs. placebo in the patients who, at the time of randomisation, still fulfilled the requirements prespecified in the protocol regarding alcohol consumption for the screening visit, using an MMRM model. Post hoc ANCOVA analyses using LOCF were also performed. Sensitivity analyses for the key secondary efficacy endpoint were performed using an LREG analysis (in which monthly observations were disregarded if there were < 14 days with data) and analyses using OC, LOCF, nonresponse, or sustained response.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	tolerability of as-needed use of nalmefene in patients with alcohol dependence		than anticipated correlations for the co-primary endpoints.	
SENSE	**Primary objective:** • To evaluate the long-term safety and tolerability of as-needed use of nalmefene vs. placebo over a period of 52 weeks • To demonstrate a difference in the treatment effect between placebo and as-needed nalmefene for change from baseline to month 6 in number of HDDs and monthly TAC (added as co-primary efficacy endpoints after protocol amendment) **Secondary objectives:** • To evaluate the effect of as-needed use of nalmefene in patients with alcohol dependence during a period of 24 weeks on: − Proportion of responders based on drinking measures − Alcohol dependence symptoms and clinical status − Liver function and other clinical safety laboratory tests − Pharmacoeconomic outcomes	All efficacy analyses were performed on the FAS. All safety analyses were performed on the APTS; pretreatment AEs were summarised for the APRS. Safety was evaluated on the basis of AEs, clinical safety laboratory tests, vital signs, weight (body mass index), ECG, and POMS score. Both co-primary efficacy variables were analysed using MMRM and OC, with the baseline 1 score as a covariate, and site, sex, time in months (months 1-13), and treatment as fixed effects, tested at the 5% level of significance. The key secondary efficacy analysis of RSDRL at month 6 used LREG, [redacted] Analyses of the co-primary endpoints and of the key	[redacted] The sample size calculation was based on a standard deviation for the change from baseline in number of HDDs of 7 days and the change from baseline in TAC of 36.5 g/day. With a significance level of 5%, 668 patients randomised 3:1 would provide power of at least 90% for detecting a standardised effect size of 3 HDDs and 12 g/day in the TAC.	Sensitivity analyses were conducted for each of the co-primary efficacy variables: an MMRM analysis (in which monthly observations were disregarded if there were < 14 days of data) and ANCOVA by month using OC, LOCF, or BOCF. Post hoc ANCOVA analyses were performed for the co-primary efficacy variables in which missing values were imputed using PMI based on the mean reduction observed at month 1 in the placebo group (adjusted for sex). Additional post hoc analyses were performed to compare the effect of nalmefene vs. placebo in the patients who, at the time of randomisation, still fulfilled the requirements prespecified in the protocol regarding alcohol consumption for the screening visit, using an MMRM model. Post hoc ANCOVA analyses using LOCF were also performed. [redacted]

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	• To evaluate the long-term therapeutic effect of as-needed nalmefene vs. placebo over a period of 52 weeks in patients with alcohol dependence on: − Reduction of alcohol consumption − Alcohol dependence symptoms and clinical status − Liver function and other clinical safety laboratory tests − Pharmacoeconomic outcomes	secondary endpoint (RSDRL) and the sensitivity analyses for both the co-primary and key secondary endpoints were repeated post hoc for the patients with a high/very high DRL at baseline and randomisation.		[redacted]

AE = adverse event; ANCOVA = analysis of covariance ; APRS = all-patients-randomised set; APTS = all-patients-treated set; BOCF = baseline observation carried forward; DRL = drinking risk level; ECG = electrocardiogram; FAS = full analysis set; HDD = heavy drinking day; IMP = investigational medicinal product; LOCF = last observation carried forward; LREG = logistic regression model; MI = multiple imputation; MMRM = mixed model repeated measures; OC = observed cases; PMI = placebo mean imputation; POMS = Profile of Mood States; RSDRL = response defined as a downward shift from baseline in DRL by two categories; TAC = total alcohol consumption.

APTS: all patients randomised excluding those with no recorded IMP intake and all IMP returned.

FAS: all patients in the APTS who had at least one valid postbaseline assessment in the main treatment period of both co-primary efficacy variables (HDDs and TAC) and had an average alcohol consumption at medium risk or above according to World Health Organization criteria (> 40 g/day for men and > 20 g/day for women) at the screening visit.

[redacted]

Source; Gual et al., 2013; Lundbeck 2012a-c, 2012e; Mann et al., 2013.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post hoc.

In ESENSE1 and ESENSE2, approximately 78% of all the enrolled patients had a high/very high DRL at baseline. In SENSE, 52% of the enrolled patients had a high/very high DRL at baseline (see Figure A1, Section 1.4).

Among patients with a high/very high DRL at baseline in ESENSE1 and ESENSE2, 74% and 57%, respectively, continued drinking at this level at randomisation. In the SENSE study, 52% of the patients drinking at high/very high DRL at baseline continued to drink at this level at randomisation (see Figure A1, Section 1.4)

Patients who considerably reduced their alcohol consumption in the period between screening (baseline) and randomisation consumed such a small amount of alcohol at randomisation that there was little room for further improvement in alcohol consumption reduction (floor effect). Although these patients stayed in the study and maintained their low level of alcohol consumption throughout the treatment period (irrespective of treatment), it may be argued that these patients were not in need of pharmacologic treatment for the management of alcohol dependence. Furthermore, the baseline characteristics of these patients were similar to those of the total population (at screening), with no apparent features that would predict their behaviour in the period between screening and randomisation. This nonspecific effect leading to considerable reduction of alcohol consumption between screening and randomisation was considered to be due to motivational elements (e.g., help-seeking behaviour and willingness to change) and to the screening interventions (discussing the patient's alcohol dependence and quantifying alcohol consumption).

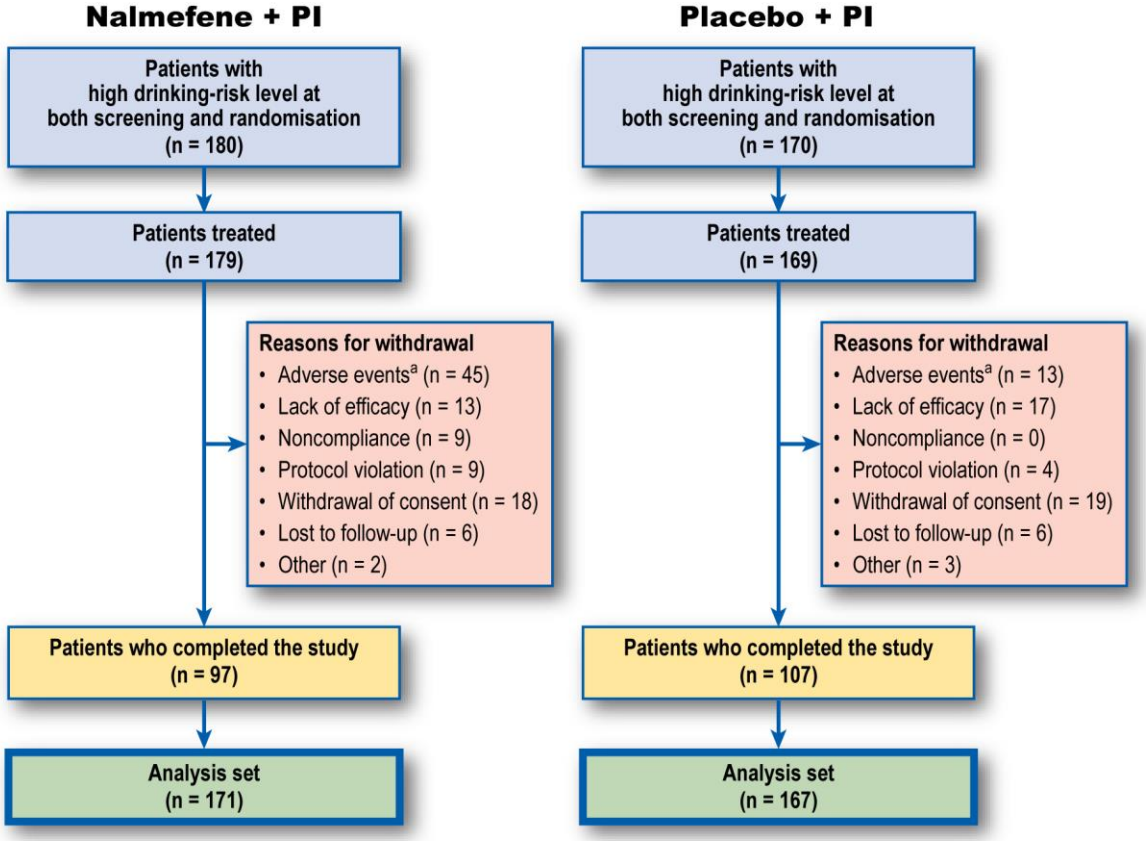
After discussion with, and with the agreement of, the SAG, post hoc subgroup analyses were performed to substantiate the clinical efficacy and the clinical relevance of nalmefene and, in particular, to define a population in which the benefit of nalmefene would be greatest. An analysis was performed in the subgroup of patients with high/very high DRL at baseline who maintained a high/very high DRL at randomisation, because these were the patients who were expected to benefit most from nalmefene. The SAG recognised the validity of the subgroup analyses and the clinical effect of nalmefene; these analyses form the basis of the nalmefene licence.

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure B4, Figure B5, and Figure B6 present the participant flow diagrams in ESENSE1, ESENSE2, and SENSE for patients with a high/very high DRL at baseline and randomisation. Section **Error! Reference source not found.**, Appendix 4 presents the participant flow diagrams for the total clinical trial population.

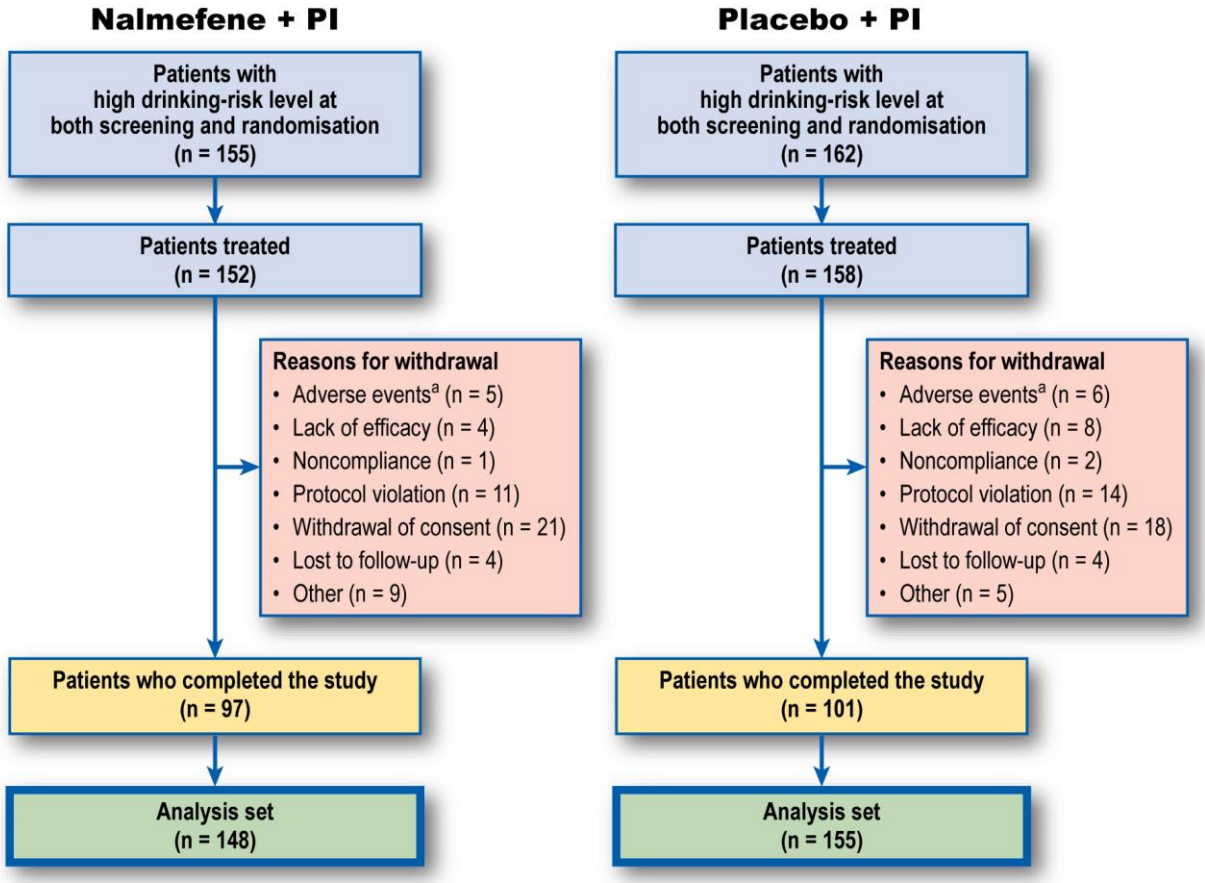
Figure B4. Patient flow chart in ESENSE1 (study 12014A): licensed population



[a] Adverse events were not by default set to primary reason for dropout.

PI = psychosocial intervention.

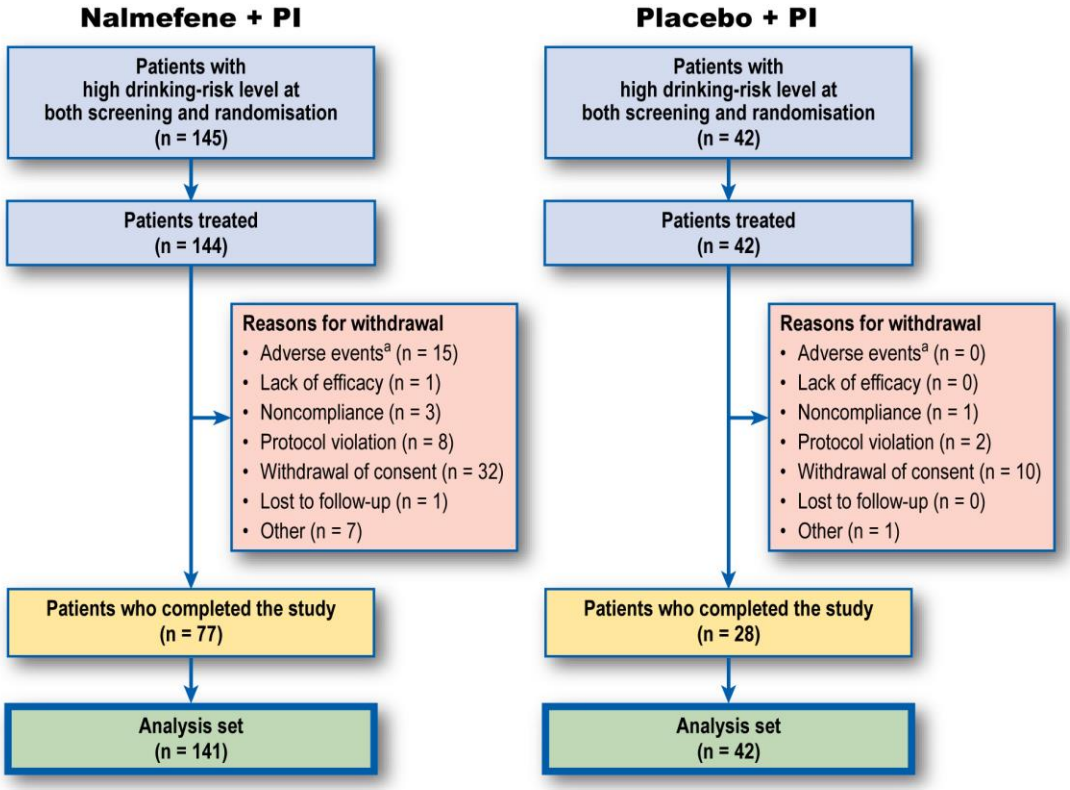
Figure B5. Patient flow chart in ESENSE2 (study 12023A): licensed population



[a] Adverse events were not by default set to primary reason for dropout.

PI = psychosocial intervention.

Figure B6. Patient flow chart in SENSE (study 12013): licensed population



[a] Adverse events were not by default set to primary reason for dropout.

PI = psychosocial intervention.

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?

- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See Section 10.3, Appendix 3 for a suggested format.

Section **Error! Reference source not found.**, Appendix 5 presents the complete quality assessment for ESENSE1, ESENSE2, and SENSE.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table B10 presents the quality assessment results for ESENSE1, ESENSE2, and SENSE.

Table B10. Quality assessment results for RCTs

Trial no. (acronym)	**Study 12014A (ESENSE1)**	**Study 12023A (ESENSE2)**	**Study 12013A (SENSE)**
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	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	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	Yes	Yes
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in healthcare. York: Centre for Reviews and Dissemination.			

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by “intention to treat.” State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Efficacy results are presented here for the licensed population (patients with a high/very high DRL at baseline and randomisation) in accordance with the product label. Sections **Error! Reference source not found.** and **Error! Reference source not found.**, Appendix 4 presents total study population results.

Primary efficacy results: ESENSE1 and ESENSE2

In the licensed population (patients with a high/very high DRL at baseline and randomisation), nalmefene reduced the number of HDDs significantly more than placebo from baseline to month 6 in both ESENSE1 and ESENSE2 (Table B11).

Table B11. Mean difference to placebo in the change from baseline to month 6 in HDDs and TAC (FAS; MMRM) in patients with a high/very high DRL at baseline and randomisation (ESENSE1 and ESENSE2): licensed population

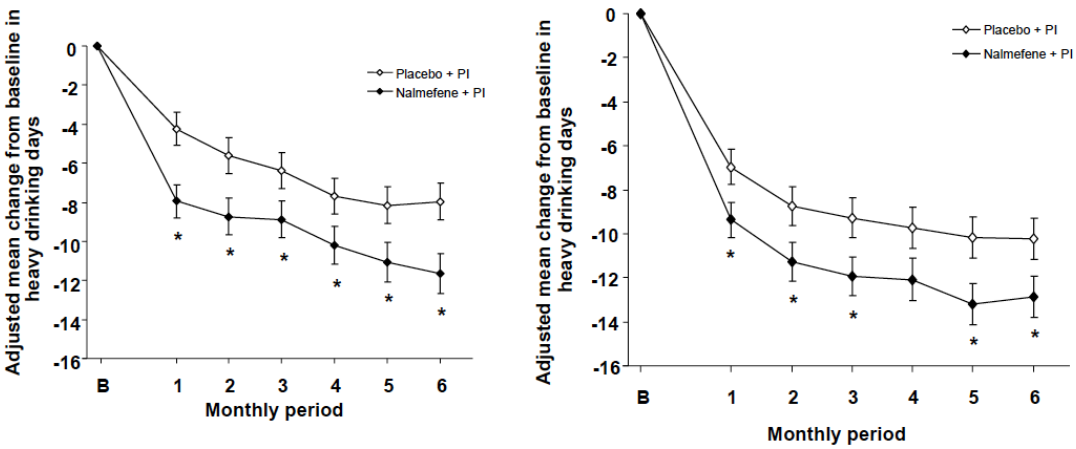
Trial	Number of participants at baseline		Endpoint	Mean difference to placebo in the change from baseline to month 6	95% CI	*P* value
	Nalmefene + PI	Placebo + PI				
ESENSE1	171	167	HDD	−3.7 days/month	−5.9 to −1.5	0.001
			TAC	−18.3 g/day	−26.9 to −9.7	< 0.001
ESENSE2	148	155	HDD	−2.7 days/month	−5.0 to −0.3	0.025
			TAC	−10.3 g/day	−20.2 to −0.5	0.040

CI = confidence interval; DRL = drinking risk level; FAS = full analysis set; HDD = heavy drinking day; MMRM = mixed model repeated measures; PI = psychosocial intervention; TAC = total alcohol consumption.

Source: Lundbeck 2012e

In both studies, the effect in favour of nalmefene was observed by month 1 and maintained throughout the study period (Figure B7). Nalmefene was significantly superior to placebo in reducing TAC at all time points measured from month 1 to month 6 in both ESENSE1 and ESENSE2 (Figure B8). For both studies, the treatment effect was larger in the licensed patient population than in the total trial population.

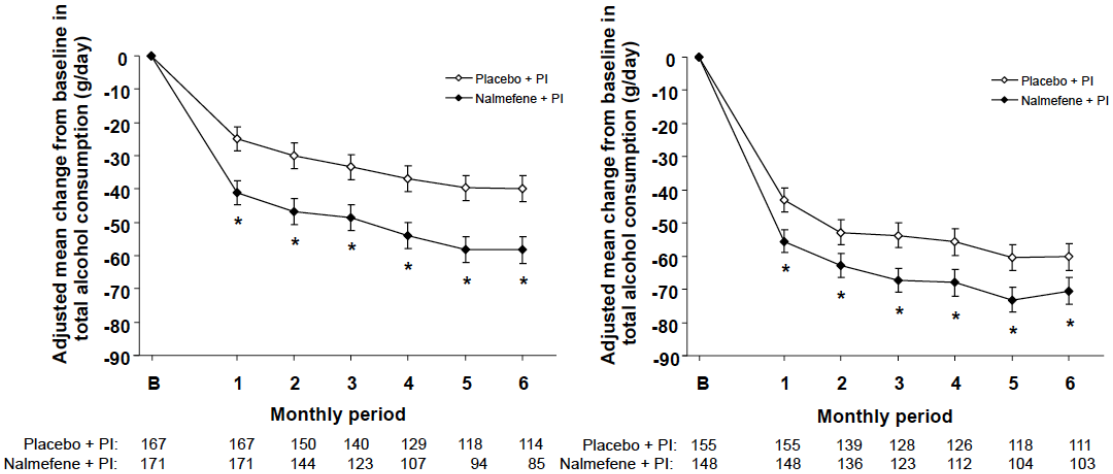
Figure B7. Change from baseline in the number of HDDs among patients with a high/very high DRL at baseline and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population



* *P* < 0.05.

DRL = drinking risk level; FAS = full analysis set; HDD = heavy drinking day; MMRM = mixed model repeated measures; PI = psychosocial intervention.

Figure B8. Change from baseline in TAC among patients with a high/very high DRL at baseline and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population



* *P* < 0.05.

DRL = drinking risk level; FAS = full analysis set; HDD = heavy drinking day; MMRM = mixed model repeated measures; PI = psychosocial intervention.

Secondary efficacy results: ESENSE1 and ESENSE2

This section contains the results for the following secondary efficacy endpoints:

- Response at month 6 (RSDRL, RLDRL [response defined as a downward shift from baseline in DRL to low DRL or lower], R70 [≥ 70% reduction in TAC])
- CGI-S and Clinical Global Impression-Global Improvement (CGI-I)
- Gamma-glutamyl transferase (GGT) and alanine aminotransferase (ALAT)
- Quality of life and utility data outcomes (36-item Short-form Health Survey [SF-36] version 2 and EuroQol-5 Dimensions [EQ-5D])
- Drinker Inventory of Consequences (DrInC-2R) total score

It is important to note that neither ESENSE1 nor ESENSE2 was powered to statistically separate the two treatment arms on these secondary endpoints.

Response at Month 6

In ESENSE1 and ESENSE2, the odds ratio (OR) for response at month 6 was in favour of nalmefene (OR > 1) for all three definitions of response proposed by the EMA guidance (EMA, 2010) (Table B12). However, these were only statistically significant for ESENSE1.

Table B12. Odds ratio for response secondary efficacy endpoints in the patients with a high/very high DRL at baseline and randomisation (FAS, MMRM): licensed population

Trial	Number of participants at baseline		Endpoint	Odds ratio for response at month 6	95% CI	*P* value
	Nalmefene + PI	Placebo + PI				
ESENSE1	171	167	RSDRL	2.15	1.38-3.36	< 0.001
			RLDRL	[redacted]	[redacted]	[redacted]
			R70	[redacted]	[redacted]	[redacted]
ESENSE2	148	155	RSDRL	1.59	0.98-2.59	0.062
			RLDRL	[redacted]	[redacted]	[redacted]
			R70	[redacted]	[redacted]	[redacted]

CI = confidence Interval; DRL = drinking risk level; FAS = full analysis set; MMRM = mixed model repeated measures; PI = psychosocial intervention; R70 = ≥ 70% reduction in total alcohol consumption; RLDRL = response defined as a downward shift from baseline in DRL to low DRL or lower; RSDRL = response defined as a downward shift from baseline in DRL by two risk categories.

Source: Lundbeck, 2012e; van den Brink et al, 2013a; van den Brink et al., 2013b.

[redacted]

An analysis of RSDRL, RLDRL, and R70 was performed post hoc in the licensed population, using pooled data from ESENSE1 and ESENSE2 (Table B13 and Figure B9):

- RSDRL: 57% of the patients in the nalmefene group and 42% of the patients in the placebo group were responders based on RSDRL at month 6 (OR for response, 1.87; 95% CI, 1.35 to 2.59).
- RLDRL: The proportion of responders was 43% in the nalmefene group and 32% in the placebo group (OR, 1.79; 95% CI, 1.27 to 2.53)
- R70: The proportion of responders was 38% in the nalmefene group and 26% in the placebo group (OR, 1.88; 95% CI, 1.32 to 2.70)

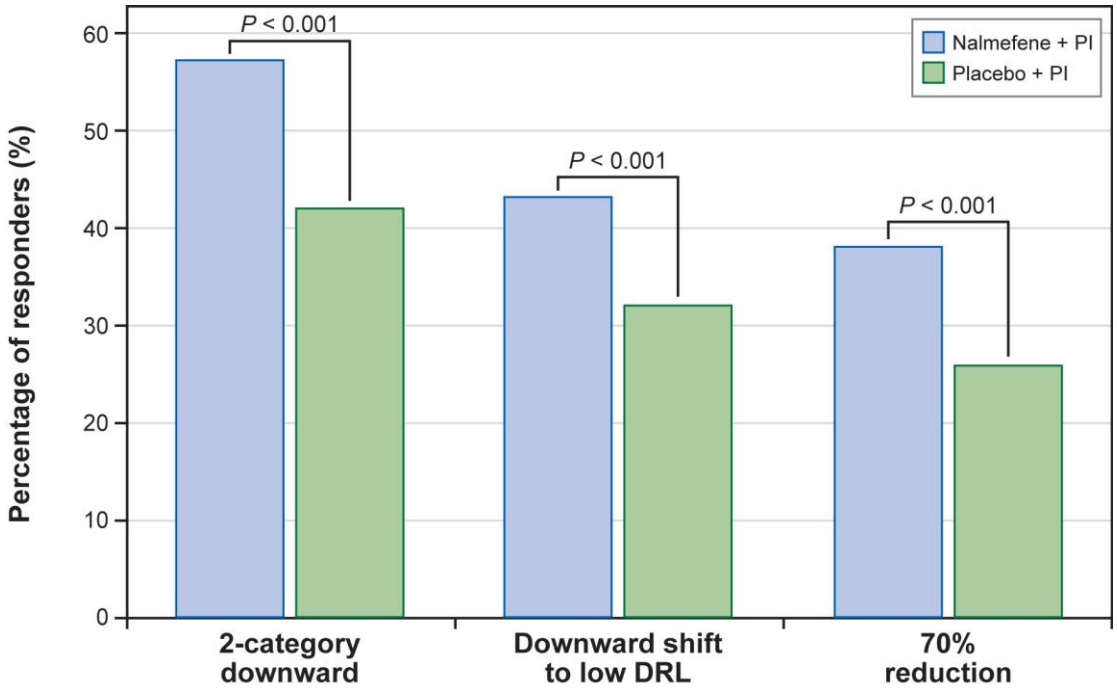
Table B13. Odds ratio for responder analysis in patients with a high/very high DRL at baseline and randomisation (FAS, MMRM) (pooled data from ESENSE1 and ESENSE2): licensed population

Responder analysis	Odds ratio	95% CI	*P* value
RSDRL	1.87	1.35-2.59	< 0.001
RLDRL	1.79	1.27-2.53	< 0.001
R70	1.88	1.32-2.70	< 0.001

CI = confidence interval; DRL = drinking risk level; FAS = full analysis set; MMRM = mixed model repeated measures; R70: ≥ 70% reduction in total alcohol consumption; RLDRL = response defined as a downward shift from baseline in DRL to low DRL or lower; RSDRL = response defined as a downward shift from baseline in DRL by two risk categories.

Source: Lundbeck, 2012e.

Figure B9. Responder analyses at 6 months for patients with high/very high DRL at baseline and randomisation (pooled data from ESENSE1 and ESENSE2): licensed population



DRL = drinking risk level.

CGI-S and CGI-I

In ESENSE1 and ESENSE2, the CGI-S and CGI-I scores in the licensed population decreased more in the nalmefene group than in the placebo group throughout the main treatment period; the differences were in favour ($P < 0.05$) of nalmefene at month 6 (Table B14, Figure B10, and Figure B11).

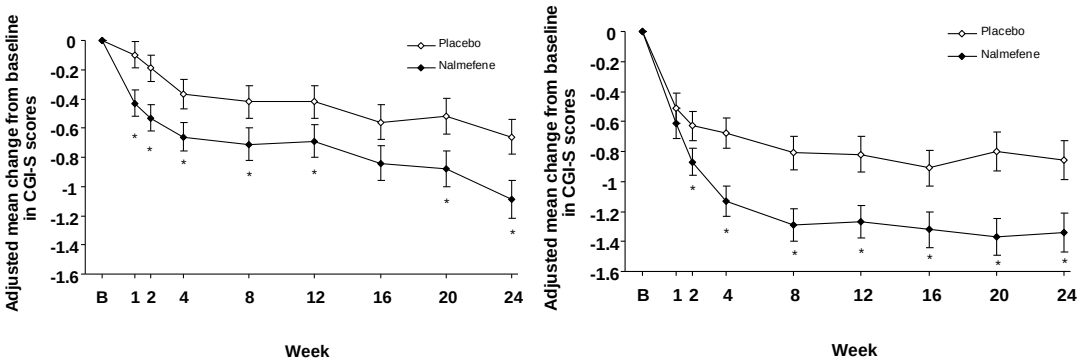
Table B14. Changes from baseline to month 6 in CGI-S and CGI-I in patients with a high/very high DRL at baseline and randomisation (FAS, MMRM) (ESENSE1 and ESENSE2): licensed population

Trial	Number of participants at baseline		Endpoint	Difference to placebo in mean change from baseline to month 6	95% CI	*P* value
	Nalmefene + PI	Placebo + PI				
ESENSE1	171	167	CGI-I	−0.6	−0.8 to −0.3	< 0.0001
			CGI-S	−0.4	−0.7 to −0.1	0.0051
ESENSE2	148	154	CGI-I	−0.3	−0.6 to −0.0	0.0425
			CGI-S	−0.5	−0.8 to −0.1	0.0050

CGI-I = Clinical Global Impression-Global Improvement; CGI-S = Clinical Global Impression-Severity; CI = confidence interval; DRL = drinking risk level; FAS = full analysis set; MMRM = mixed model repeated measures; PI = psychosocial intervention.

Source: Lundbeck, 2012e; van den Brink et al, 2013a; van den Brink et al., 2013b.

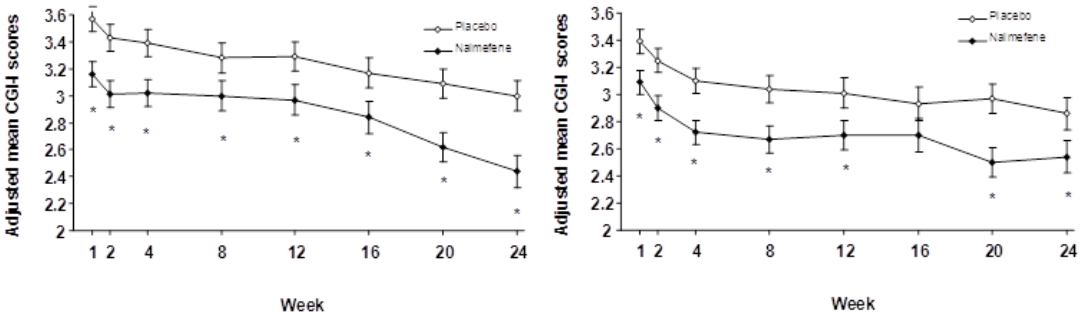
Figure B10. Change from baseline in CGI-S in patients with a high/very high DRL at baseline and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population



* $P < 0.05$.

CGI-S = Clinical Global Impression-Severity; DRL = drinking risk level; FAS = full analysis set; MMRM = mixed model repeated measures.

Figure B11. Change from baseline in CGI-I in patients with a high/very high DRL at baseline and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population



* *P* < 0.05.

CGI-I = Clinical Global Impression-Global Improvement; DRL = drinking risk level; FAS = full analysis set; MMRM = mixed model repeated measures.

GGT and ALAT

In ESENSE1 and ESENSE2, the reduction in alcohol consumption in patients with a high/very high DRL at baseline and randomisation following treatment with nalmefene translated into a greater decrease in liver enzymes (GGT and ALAT) relative to placebo.

In both studies, the mean GGT values in the licensed population decreased more from baseline to month 6 in the nalmefene group than in the placebo group; the difference was significantly in favour (*P* < 0.05) of nalmefene in ESENSE1 (Table B15).

Table B15. GGT mean change compared with placebo at month 6 in patients with high/very high DRL at screening and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population

Treatment group	Baseline		Month 6		Mean change compared with placebo at month 6		
	N	Mean (IU/L)	N	Mean (IU/L)	Ratio of NMF:PBO	95% CI	*P* value
ESENSE1							
NMF + PI	171	55.7	87	39.5	0.73	0.64-0.84	< 0.001
PBO + PI	167	60.1	112	53.9	—	—	—
ESENSE2							
NMF + PI	148	55.9	100	47.3	0.90	0.76-1.07	0.244
PBO + PI	153	54.9	108	52.4	—	—	—

CI = confidence interval; DRL = drinking risk level; FAS = full analysis set; GGT = gamma-glutamyl transferase; MMRM = mixed model repeated measures; NMF = nalmefene; PBO = placebo; PI = psychosocial intervention.

Source: Lundbeck, 2012e.

In ESENSE1 and ESENSE2, the mean ALAT values in the licensed population decreased more from baseline to month 6 in the nalmefene group than in the placebo group; the differences were significantly in favour ($P < 0.05$) of nalmefene in both studies (Table B16).

Table B16. ALAT mean change compared with placebo at month 6 in patients with high/very high DRL at screening and randomisation in ESENSE1 and ESENSE2 (FAS, MMRM): licensed population

Treatment group	Baseline		Month 6		Mean change compared with placebo at month 6		
	N	Mean (IU/L)	N	Mean (IU/L)	Ratio NMF:PBO	95% CI	*P* value
ESENSE1							
NMF + PI	171	29.4	87	24.7	0.83	0.75; 0.93	0.001
PBO + PI	166	29.3	110	29.6	—	—	—
ESENSE2							
NMF + PI	148	29.3	100	26.8	0.85	0.75; 0.96	0.010
PBO + PI	153	29.0	108	31.5	—	—	—

ALAT = alanine aminotransferase; CI = confidence interval; DRL = drinking risk level; FAS = full analysis set; MMRM = mixed model repeated measures; NMF = nalmefene; PBO = placebo; PI = psychosocial intervention.

Source: Lundbeck, 2012e.

Quality of life and utility data outcomes

In ESENSE1 and ESENSE2, the baseline SF-36 and EQ-5D scores were similar for both the nalmefene and placebo treatment groups (Table B17). The mean SF-36 component summary scores in the licensed population increased (i.e., improved) from baseline to month 6 in the nalmefene group to a greater extent than in the placebo group in both ESENSE1 and ESENSE2 studies. The differences were not statistically significant in ESENSE1, but both the physical and mental component scores in ESENSE2 were significantly in favour of nalmefene (Table B17).

Table B17. SF-36 component summary 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

Treatment group	Baseline, mean (SD)	Change from baseline to month 6, mean (SD)	Difference to PBO, mean (SD)	95% CI (*P* value)
ESENSE1				
Physical component				
NMF + PI	[redacted]	[redacted]	[redacted]	[redacted]
PBO + PI	[redacted]	[redacted]	[redacted]	[redacted]
Mental component				
NMF + PI	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + PI	[redacted]	[redacted]	[redacted]	[redacted]
ESENSE2				
Physical component				
NMF + PI	[redacted]	[redacted]	[redacted]	[redacted]
PBO + PI	[redacted]	[redacted]	[redacted]	[redacted]
Mental component				
NMF + PI	[redacted]	[redacted]	[redacted]	[redacted]
PBO + PI	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DRL = drinking risk level; FAS = full analysis set; PBO = placebo; PI = psychosocial intervention; NMF = nalmefene; SD = standard deviation; SF-36 = 36-item Short-form Health Survey.

Number of patients: ESENSE1, PBO = 166, NMF = 167; ESENSE2, PBO = 148, NMF = 146.

Source: Lundbeck, 2012e.

[redacted]

For the pooled analysis of ESENSE1 and ESENSE2, the SF-36 mental component score change from baseline to month 6 was significantly higher for the nalmefene group compared with placebo: the mean (SD) change from baseline was 5.74 (0.79) in the nalmefene group and 2.65 (0.78) in the placebo group, a mean difference of 3.09 (0.92; *P* = 0.0008) (Table B18). The improvement at month 6 was also significantly larger for the nalmefene group compared with the placebo group for the physical component score (incremental of 1.23 ± 0.55; *P* = 0.0259) (Table B18).

Table B18. SF-36 adjusted mean change from baseline to month 6 in pooled ESENSE1 and ESENSE2 (MMRM, FAS): observed cases– licensed population

	Change from baseline to month 6			Difference to placebo		
Score	**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.

A lower score indicates fewer alcohol-related problems.

In ESENSE1 and ESENSE2, the EQ-5D health state and utility index score in the licensed population increased more from baseline to month 6 in the nalmefene group than in the placebo group. This was statistically significant in favour of nalmefene for the health state score in ESENSE1 only (Table B19).

Table B19. 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

Treatment group	Baseline, mean (SD)	Change from baseline to month 6, Mean (SD)	Difference to PBO, mean (SD)	95% CI, (*P* value)
ESENSE1				
Health state				
NMF + PI	[redacted]	[redacted]	[redacted]	[redacted]
PBO + PI	[redacted]	[redacted]	[redacted]	[redacted]
Utility index				
NMF + PI	[redacted]	[redacted]	[redacted]	[redacted]
PBO + PI	[redacted]	[redacted]	[redacted]	[redacted]
ESENSE2				
Health state				
NMF + PI	[redacted]	[redacted]	[redacted]	[redacted]
PBO + PI	[redacted]	[redacted]	[redacted]	[redacted]
Utility index				
NMF + PI	[redacted]	[redacted]	[redacted]	[redacted]
PBO + PI	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DRL = drinking risk level; EQ-5D = EuroQol-5 Dimensions; FAS = full analysis set; MMRM = mixed model repeated measures; NMF = nalmefene; PBO = placebo; PI = psychosocial intervention.

Number of patients: ESENSE1, PBO = 164 and 166 (health state and utility index, respectively); NMF = 170. ESENSE2, PBO = 151 and 152 (health state and utility index, respectively); NMF = 147.

Source: Lundbeck, 2012e.

[redacted]

For the pooled analysis, the mean change from baseline for nalmefene compared with placebo was 3.46 points (*P* = 0.0124) for the health state score and 0.03 points (*P* = 0.0445) for the utility index score (Table B20) (Lundbeck, 2012d; François et al., 2013). These differences in utility index score between nalmefene and placebo are similar to those observed in an observational longitudinal study in patients with alcohol dependence who shifted to lower alcohol consumption and fewer alcohol-related problems (Gunther et al., 2008; Lundbeck, 2012d).

Table B20. EQ-5D adjusted mean change from baseline to month 6 in pooled ESENSE1 and ESENSE2 (MMRM, FAS): observed cases– licensed population

	Change from baseline to month 6			Difference to placebo		
Score	**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.

A lower score indicates fewer alcohol-related problems.

Drinker Inventory of Consequences (DrInC-2R) total score

The DrInC is a questionnaire designed to measure adverse consequences of alcohol abuse in five areas: interpersonal, physical, social, impulsive, and intrapersonal. Each scale provides a lifetime and past 3-month measure of adverse consequences, and scales can be combined to assess total adverse consequences. Pooling ESENSE1 and ESENSE2, the mean DrInC-2R total score change from baseline to month 6 was significantly correlated to HDD and TAC reduction (*P* < 0.0001). The improvement, indicating fewer alcohol-related problems, was significantly larger with nalmefene (17.86 ± 1.31) than with placebo (14.64 ± 1.30) (*P* = 0.0292) (Table B21).

Table B21. DrInC-2R adjusted mean change from baseline to month 6 in ESENSE1 and ESENSE2 pooled (MMRM, FAS): observed cases– licensed population

	Change from baseline to month 6			Difference to placebo		
Score	**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; FAS = full analysis set; MMRM = mixed model repeated measures; NMF = nalmefene; PBO = placebo; PI = psychosocial intervention; SE = standard error.

A lower score indicates fewer alcohol-related problems.

Efficacy Results: SENSE

Efficacy analyses were secondary endpoints for the SENSE safety study. The effects of nalmefene on the number of HDDs and TAC were larger in the licensed patient population than in total trial population for SENSE.

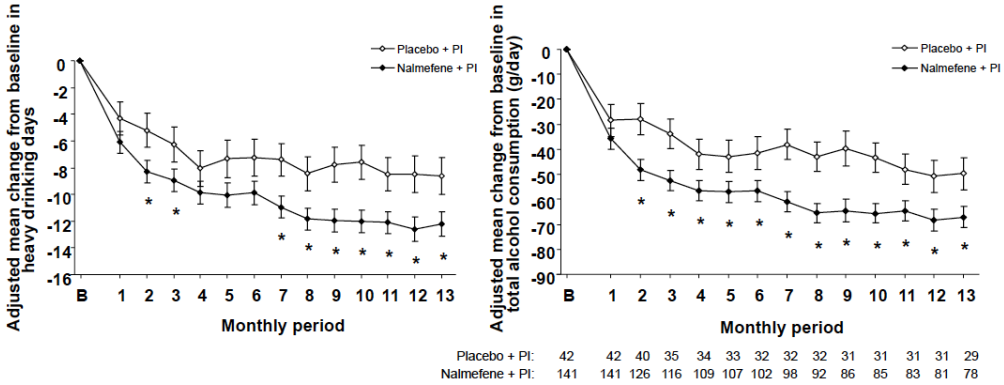
In the licensed patient population, nalmefene reduced the number of HDDs and TAC consistently more than placebo throughout the 1-year treatment period (Table B22 and Figure B12). At month 6, the mean difference to placebo was −2.6 HDDs/month (95% CI, −5.5 to 0.2; *P* = 0.071) and −15.3 g/day (95% CI, −29.1 to −1.5; *P* = 0.031). At month 13, the mean difference to placebo in the number of HDDs was −3.6 days/month (95% CI, −6.5 to −0.7; *P* = 0.016) and the mean difference to placebo in TAC was −17.3 g/day (95% CI, −30.9 to −3.8; *P* = 0.013) in favour of nalmefene. The difference in treatment effect between nalmefene and placebo persisted throughout the treatment period and even increased with time, indicating that tolerance to the effectiveness of nalmefene did not develop within at least 12 months of treatment.

Table B22. Mean difference to placebo in the change from baseline to month 6 or month 13 in HDDs and TAC (FAS, MMRM) in patients with a high/very high DRL at baseline and randomisation (SENSE): licensed population

	Number of participants at baseline		Endpoint	Mean difference to PBO in the change from baseline to month 6 or 13	95% CI	*P* value
	NMF + PI	PBO + PI				
SENSE (Month 6)	141	42	HDD	−2.6 HDDs/month	−5.5 to 0.2	0.071
			TAC	−15.3 g/day	−29.1 to −1.5	0.031
SENSE (Month 13)	141	42	HDD	−3.6 HDDs/month	−6.5 to −0.7	0.016
			TAC	−17.3 g/day	−30.9 to −3.8	0.013

CI = confidence interval; DRL = drinking risk level; FAS = full analysis set; HDD = heavy drinking day; MMRM = mixed model repeated measures; NMF = nalmefene; PBO = placebo; PI = psychosocial intervention; TAC = total alcohol consumption.

Figure B12. Change from baseline to month 13 in the number of HDDs and TAC observed among patients with a high/very high DRL in SENSE (FAS, MMRM): licensed population



* *P* < 0.05.

DRL = drinking risk level; FAS = full analysis set; HDD = heavy drinking day; MMRM = mixed model repeated measures; PI = psychosocial intervention; TAC = total alcohol consumption.

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's "Guide to the methods of technology appraisal," Sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

A meta-analysis has not been conducted for the specific purpose of this NICE submission. However, individual patient data from ESENSE1, ESENSE2, and SENSE were pooled for analysis purposes. 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.

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable

6.6.3 If any of the relevant RCTs listed in response to Section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Not applicable

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's "Guide to the methods of technology appraisal," Sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.4, Appendix 4.

As described in Section 6.1.1, two systematic reviews were conducted for this submission:

- One systematic review was performed to identify studies evaluating the pharmacological agents nalmefene and naltrexone for reduction of alcohol consumption in actively drinking alcohol-dependent patients.

- A second systematic review was conducted to identify clinical trials investigating psychosocial interventions listed in the scope for nalmefene, in addition to interventions listed in NICE CG115 that were most similar to BRENDA, the psychosocial treatment used in the nalmefene studies.

This section presents the naltrexone studies identified in the systematic review for pharmacological agents, as well as the systematic review for psychosocial interventions.

Systematic review of naltrexone studies

A systematic literature review was undertaken to identify naltrexone studies published in English from database start to October 2013. The objective of the systematic literature review was to identify the available evidence on naltrexone when used in the same context as nalmefene (alcohol reduction), and determine whether an indirect comparison could be conducted to investigate the effect of naltrexone versus nalmefene when used in actively drinking patients with mild alcohol dependence aiming for reduction of alcohol consumption.

The systematic review approach has previously been described in Section 6.1, and the corresponding search strategy and details of the search protocol reported in Section **Error! Reference source not found.**, Appendix 3.

The eligibility criteria for level 1 screening of titles/abstracts remain the same as described in Table B1 in Section 6.2.1. However, at level 2 screening of titles and abstracts, only studies investigating naltrexone were included (the level 2 screening for studies investigating nalmefene is described in Section 6.2.1, Table B2). Studies relating to nalmefene, acamprosate, or other pharmacological comparators were excluded for this review.

Table B23 presents the eligibility criteria for level 2 screening used in the systematic review of studies investigating naltrexone.

Table B23. Level 2 eligibility criteria used in the search strategy for the selection of studies assessing naltrexone

	Inclusion criteria	Exclusion criteria
Population	As per level 1 criteria (see Section 6.2.1, Table B2)	• As per level 1 criteria (see Section 6.2.1, Table B2) • Patients who are abstinent for a prespecified period for randomisation in the study • Patients with a comorbid disorder in addition to the diagnosis of alcohol dependence (e.g., schizophrenia or bipolar disorder) • Patients with coaddiction along with alcohol dependency (e.g., cocaine codependence or pathologic gambling)
Interventions	Treatment with oral naltrexone 50 mg in conjunction with any type of psychosocial support	• Naltrexone used at a dosage other than 50 mg • Extended-release naltrexone
Comparator	• Nalmefene in conjunction with any type of psychosocial support • Placebo in conjunction with any type of psychosocial support or best supportive care	None specified
Outcomes	• Studies reporting endpoints of level and/or pattern of alcohol consumption	None specified
Study design	• As per level 1 criteria (see Section 6.2.1, Table B2) • Randomised controlled trials • Studies assessing the level of alcohol consumption in the study population	• Studies that had a detoxification or alcohol-withdrawal process period before randomisation • Studies only reported as abstract or poster

Systematic review for psychosocial intervention studies

The second systematic review conducted for this submission was undertaken to identify clinical trials investigating psychosocial interventions used in alcohol dependence. The purpose of this review was to provide an update of the comprehensive review of psychosocial comparators that NICE conducted in March 2010 (NICE, 2011a), with a focus on interventions specifically listed in the scope for nalmefene, in addition to interventions listed in NICE CG115 that were most similar to BRENDA, the psychosocial treatment used in the nalmefene studies (see Section **Error! Reference source not found.**, Appendix 6, for further details).

The psychosocial interventions considered to be most similar to BRENDA included planned brief interventions and motivational interventions. Results

from a recent survey conducted by Lundbeck indicate that brief interventions are the mainstay of treatment for alcohol dependence in primary and specialist care in England (Lundbeck data on file, 2014). In this survey, responses were received from more than 20 primary care practices and specialist alcohol centres/addiction clinics from across England. In primary care, brief intervention is the mainstay of treatment and mostly consists of brief advice, given by the GP or practice nurse, to cut down or abstain from drinking. In some practice areas, the brief intervention is supplemented by a variety of low-intensity offerings, including psychosocial support of an unspecified nature, group therapy, a physical health check, and/or vitamin supplementation.

In specialist alcohol and addiction centres, a wider range of options is available, with the intervention being offered varying considerably from patient to patient. Even in these specialist centres, brief interventions are routinely available for 80% to 100% of patients. Other psychosocial interventions offered at specialist centres include cognitive behavioural therapies: these were available in four of the specialist centres surveyed and may be offered to up to 20% to 30% of patients in that setting. Other more intensive interventions used in a minority of patients in specialist centres include behavioural therapies, behavioural self-control training, aversion therapy, counseling, cue exposure, and behavioural and network therapy.

The psychosocial interventions included in the systematic review are listed below:

- Cognitive behavioural therapies
- Behavioural therapies
- Social network and environment therapies
- Brief interventions
- Motivational enhancement therapy

MEDLINE (via PubMed platform), EMBASE (via Dialog platform), Cochrane Library, and PsycINFO databases were searched to identify English-language studies. The searches were restricted to September 2009, which allowed a 6-month overlap from when the searches were conducted for NICE CG115 (NICE, 2011a). The full search strategy is presented in Section **Error! Reference source not found.**, Appendix 3.

Bibliographies of included systematic reviews and meta-analyses were searched for additional relevant clinical studies. Bibliographies of accepted studies were also reviewed to identify other potentially relevant references.

The eligibility criteria for level 1 and level 2 screening are presented in Table B24 and Table B25, respectively.

Table B24. Level 1 eligibility criteria used in the search strategy

Criteria	Included	Excluded
	Population	• Adults (≥18 years) with alcohol dependence • Children (aged <18 years)
Interventions	• Brief interventions (planned only) − e.g., psychoeducational and motivational techniques • Cognitive behavioural therapies: − Standard cognitive behaviour therapy − Coping skills − Social skills training − Relapse prevention • Behavioural therapies: − Cue exposure − Behavioural self-control training − Contingency management − Aversion therapy • Motivational enhancement therapy • Social network and environment therapies: − Social behaviour and network therapy − Community reinforcement approach	• None specified
	Outcomes	• None specified[b] • None specified
Study design	• Parallel-group, randomised controlled prospective clinical trials (triple/double/single-blind or open label) • Cross-over, randomised controlled prospective clinical trials (triple/double/single-blind or open label) • Non–randomised controlled clinical trials • Long-term follow-up studies (e.g., open-label follow-up of randomised clinical trials) • Prospective cohort studies and longitudinal studies • Retrospective cohort studies and longitudinal studies • Case-control studies • Cross-sectional studies • Systematic reviews and meta-analyses[a]	• Preclinical studies • Phase 1 studies • Noncomparative phase 2 trials • Prognostic studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Nonsystematic reviews • Genetic studies

[a] Systematic reviews and meta-analyses will not be included in their own right but will be used for identification of primary studies.

[b] Note that studies may report the level of alcohol consumption differently than for the nalmefene studies, but these should still be included (e.g., grams per week; drinks per day; drinks per drinking days). Furthermore, these endpoints of level of alcohol

Criteria	Included	Excluded
	consumption may be reported as secondary endpoints, with the primary endpoint being an "abstinence" endpoint (e.g., relapse to heavy drinking),. but the paper article shows that the patients were actively -drinking at baseline.	

Table B25. Level 2 eligibility criteria used in the search strategy

Criteria	Included	Excluded
Population	• Criteria in Table B24	• Criteria in Table B24 • Patients who do not have alcohol dependency (subtype of alcohol use disorder/alcohol misuse/alcohol abuse) • Patients who are abstinent or not actively drinking at randomisation • Patients with a comorbid disorder in addition to the diagnosis of alcohol dependence (e.g., schizophrenia or bipolar disorder) • Patients with coaddiction along with alcohol dependency (e.g., cocaine codependence or pathologic gambling)
Interventions	• Criteria in Table B24	• Criteria in Table B24
Outcomes[a]	• Studies reporting endpoints of level and/or pattern of alcohol consumption	• Criteria in Table B24 • Studies that do not state the level of alcohol consumption of the study population
Study design	• Criteria in Table B24 • Randomised controlled trials • Studies assessing the level of alcohol consumption in the study population	• Criteria in Table B24 • Studies with the objective of detoxifying the patients or achieving abstinence in the patients • Studies only reported as abstract or poster
[a] Note that studies may report the level of alcohol consumption differently than for the nalmefene studies, but these should still be included (e.g., grams per week; drinks per day; drinks per drinking days). Furthermore, these 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 article shows that the patients were actively drinking at baseline.		

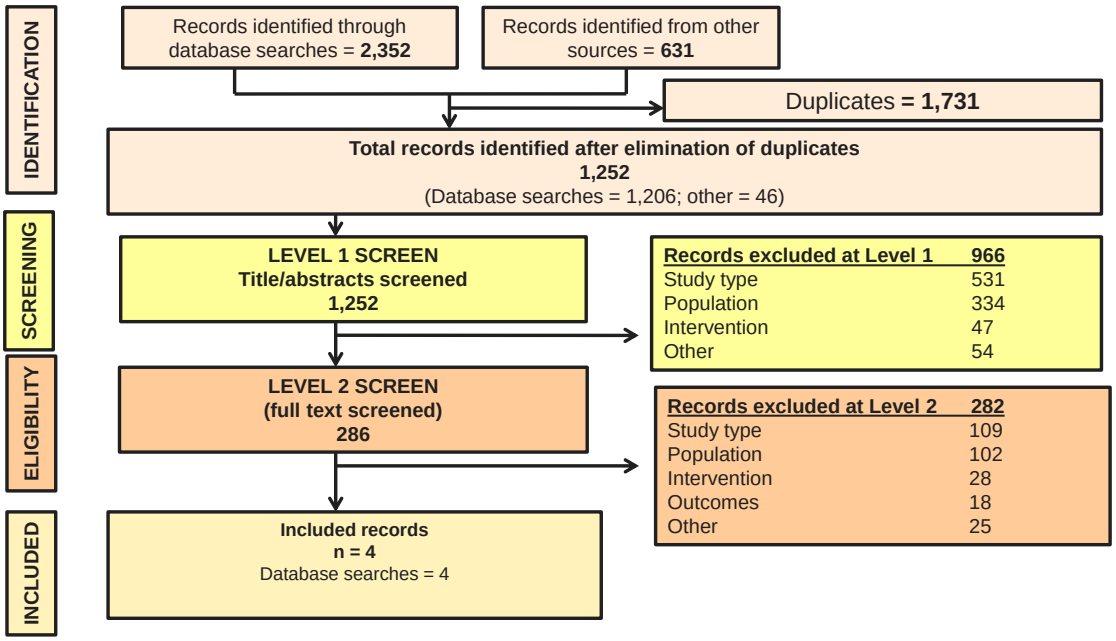
6.7.2 Please follow the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in Section 10.5, Appendix 5, a complete quality assessment for each comparator RCT identified.

Systematic review of naltrexone studies

Figure B13 describes the study attrition results for quantitative analysis in a PRISMA diagram. As described in Sections 6.2.1 and 6.7.1, the eligibility criteria for level 1 screening of titles/abstracts were the same for nalmefene and naltrexone studies. As described in Section 6.2.2, the literature search

yielded 1,252 relevant citations, once duplicates between databases and Internet sources were removed, and a total of 966 records were excluded at level 1 screening of titles/abstracts. At level 2 screening, only studies of oral naltrexone 50 mg were included. After level 2 screening, 282 articles were excluded, particularly because of nonrelevant study type (n = 109) or nonrelevant population (n = 102). After applying the level 1 and level 2 screening criteria, four articles describing two studies evaluating oral naltrexone 50 mg in alcohol dependence were included and extracted.

Figure B13. Flow diagram of identification process for systematic review (naltrexone)

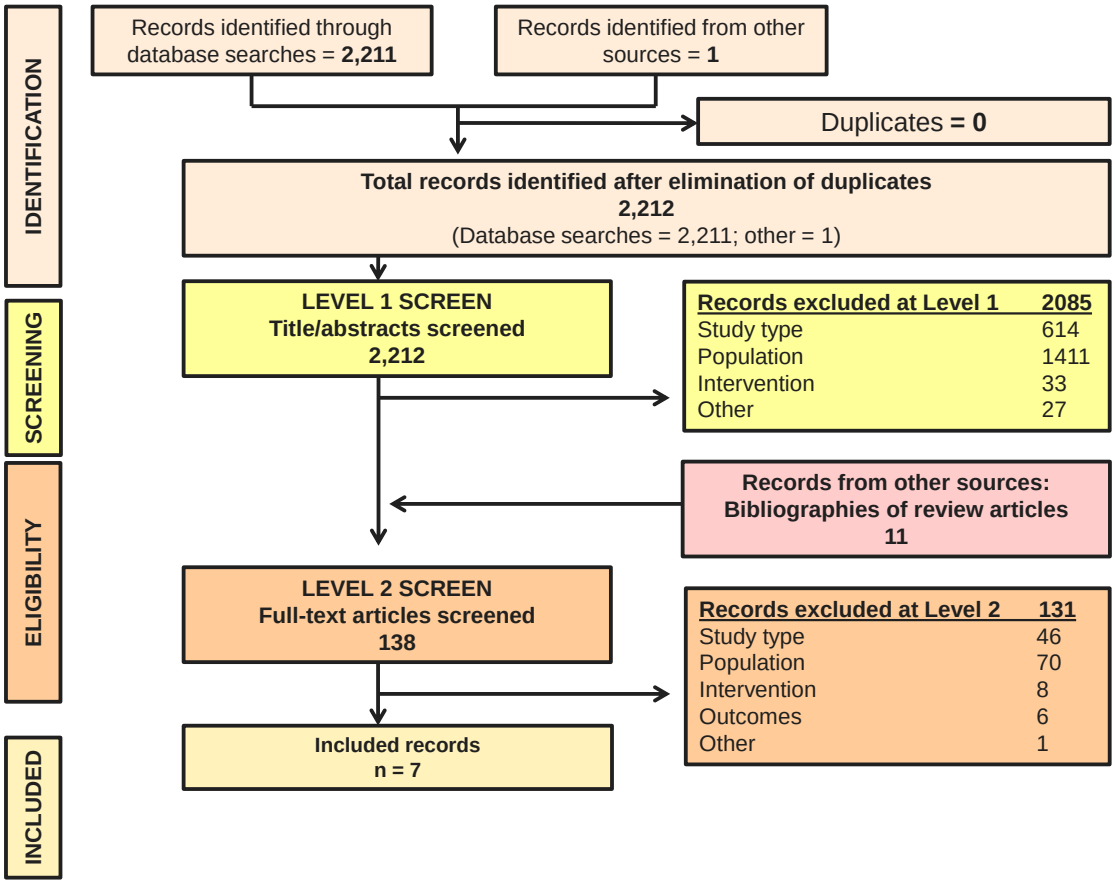


Systematic review of psychosocial interventions studies

Figure B14 presents flow diagram of the selection process for new articles of relevant psychosocial interventions as aligned with the review criteria.

The literature search yielded 2,212 relevant citations, once duplicates between databases and Internet sources were removed, and a total of 2,085 records were excluded at level 1 screening of titles/abstracts. A total of 131 records were excluded at level 2 screening. After full-text review, 7 studies met the inclusion criteria and will be used to update the previous NICE review from March 2010 (NICE, 2011a).

Figure B14. Flow diagram of identification process for systematic review update (psychosocial interventions)



6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Systematic review of naltrexone studies

According to the EMA guidelines on the development of medicinal products for alcohol dependence, the ultimate treatment goal in harm reduction studies is a clinically significant reduction in alcohol intake with subsequent harm reduction (EMA, 2009). The primary efficacy outcomes assessed in these studies, as recommended by the EMA, include change from baseline in TAC, and reduction in HDD (EMA, 2009).

In order to perform an indirect comparison of nalmefene versus naltrexone when used in actively drinking mildly alcohol-dependent patients with a treatment goal of reducing consumption, the following drinking outcomes of relevance were considered:

- Level of alcohol consumption
- Number of drinks/day
- Number of HDDs
- Percent HDDs

These drinking outcomes of relevance were selected based on the EMA guideline recommendations regarding harm reduction studies (EMA, 2010).

The following drinking outcomes were not considered as relevant endpoints for studies assessing treatment for maintenance of abstinence (EMA, 2010):

- Number of drinks per drinking day
- Number of drinking days
- Percent drinking days
- Time to first HDD
- Proportion of patients who return to heavy drinking

The systematic review identified four naltrexone articles reporting three studies (Table B26). The identified articles compared naltrexone + PI with placebo + PI: as mentioned in Section 6.2.4, no study comparing nalmefene versus naltrexone was identified.

Table B26. Overview of identified naltrexone studies

Study	Note
Heinälä et al., 2001	Randomised controlled trial
Kranzler et al., 2003	Randomised controlled trial
Hernandez-Avila et al., 2006	This reference presents a secondary analysis of the data of Kranzler et al. (2003).
Kranzler et al., 2009	Randomised controlled trial

Table B27 summarises the identified naltrexone studies, focusing on outcomes relevant for the decision problem, which is to compare naltrexone + PI versus nalmefene + PI in actively drinking alcohol-dependent patients who do not have physical withdrawal symptoms, who do not require immediate detoxification, and for whom the treatment approach is medically safe and appropriate.

The naltrexone studies failed to show significant results for relevant endpoints in reduction.

Table B27. Summary of identified naltrexone trials: study design and outcomes

<table>
<tr><th>Reference; study design; study outcomes reported; relevant drinking outcomes</th><th>Relevant drinking outcomes: study results and conclusions</th></tr>
<tr><td>Heinälä et al., 2001

In this study, conducted in Finland, 121 nonabstinent outpatients with alcohol dependence were treated with sessions of cognitive behavioural therapy (CBT) or supportive therapy (SBT) and either naltrexone 50 mg/day or placebo daily for the first 12 weeks and thereafter with targeted medication for 20 weeks in a prospective, single-centre, dual, double-blind, randomised clinical trial.

Treatment groups:
Naltrexone/CBT: 34
Placebo/CBT: 33
Naltrexone/SBT: 29
Placebo/SBT: 25

Study outcomes: Relapse to heavy drinking, alcohol consumption, craving, safety, withdrawals, compliance

Relevant drinking outcomes: Alcohol consumption (grams/week)</td>
<td>Study Results
Grams/week of alcohol consumed for the last 8 weeks of the study at the end of the study (week 32)

<table>
<tr><th>Interventions</th><th>Mean ± SD; Range (Evaluable N)</th></tr>
<tr><td>Naltrexone + CBT</td><td>231 ± 40 (34)</td></tr>
<tr><td>Naltrexone + SBT</td><td>357 ± 81 (29)</td></tr>
<tr><td>Placebo + CBT</td><td>354 ± 62 (33)</td></tr>
<tr><td>Placebo + SBT</td><td>326 ± 80 (25)</td></tr>
</table>

Study Conclusions
Conflicting results: naltrexone is worse than placebo when used with SBT and better when used with CBT (no demonstration of significant effect). This study has not demonstrated a higher efficacy of naltrexone versus placebo in reduction.</td></tr>
</table>

Reference; study design; study outcomes reported; relevant drinking outcomes	Relevant drinking outcomes: study results and conclusions
Kranzler et al., 2003 Hernandez-Avila et al., 2006 This 8-week, randomised, double-blind, placebo-controlled pilot study conducted in the United States assessed the effectiveness of naltrexone and heavy drinking among early-problem alcohol-dependent drinkers (78.7% alcohol dependent). Patients were randomly assigned to receive treatment with naltrexone (50 mg/day) or placebo and to a targeted or daily schedule of drug administration. All subjects also received brief CST. **Treatment groups:** Daily naltrexone/CST: 35 Targeted naltrexone/CST: 43 Daily placebo/CST: 39 Targeted placebo/CST: 36 **Study outcomes:** Number of drinks/day, percent drinking days, percent heavy drinking days, safety, compliance, withdrawals **Relevant drinking outcomes:** Number of drinks/day, percent heavy drinking days	**Study Results** Relevant drinking outcomes were only discussed qualitatively based on correlation analyses. The authors explained: *Although naltrexone did not significantly reduce drinking days, as hypothesized, naltrexone was better than placebo in reducing the frequency of heavy drinking during the treatment period.* *[…]* *These interactions indicate that, during the first and third weeks of treatment, the reduction in drinking in the targeted naltrexone group was greater than that in the targeted placebo group; however, during the last week of treatment, the targeted naltrexone group reported greater average alcohol consumption than did the targeted placebo group.* *[…]* *Although compared with daily placebo, daily naltrexone did not significantly reduce drinking (t = −1.24, P = 0.11).* *[…]* *Although the effects of targeted naltrexone were significantly greater than those for targeted placebo early in the study, the difference was not maintained.* **Study Conclusions** This study has not demonstrated a higher efficacy of naltrexone versus placebo in reduction of alcohol consumption. Additionally, the lack of reported data makes using this study to compare the efficacy of naltrexone versus nalmefene impossible.

Reference; study design; study outcomes reported; relevant drinking outcomes	Relevant drinking outcomes: study results and conclusions
Kranzler et al., 2009 This 12-week, randomised, double-blind, placebo-controlled pilot study conducted in the United States assessed the effectiveness of naltrexone on daily and heavy drinking among early-problem alcohol-dependent drinkers (95.1% alcohol dependent). Patients were randomly assigned to receive treatment with naltrexone (50 mg/day) or placebo and to a targeted or daily schedule of drug administration. All subjects also received brief CST. **Treatment groups:** Daily naltrexone/CST: 45 Targeted naltrexone/CST: 38 Daily placebo/CST: 41 Targeted placebo/CST: 39 **Study outcomes:** Number of drinks per day, number of drinks per drinking day, safety, compliance, withdrawals **Recent drinking outcomes:** Number of drinks/day	**Study Results** Data for the number of drinks per day were reported separately for males and females with a graphical representation of data. These data were extracted from the graphs using Engauge Digitizer 4.1 software. **Summary of number of drinks per day in males**

Interventions	Mean (SEM)						
	Baseline	2 wks	4 wks	6 wks	8 wks	10 wks	12 wks
Naltrexone + CST; daily	—	4.49 (0.23)	4.33 (0.25)	4.92 (0.36)	4.59 (0.32)	4.02 (0.26)	4.01 (0.23)
Naltrexone + CST; targeted	—	3.61 (0.22)	3.51 (0.24)	3.01 (0.16)	2.76 (0.16)	2.39 (0.15)	2.35 (0.13)
Placebo + CST; daily	—	3.94 (0.18)	3.83 (0.18)	3.56 (0.14)	3.60 (0.18)	3.16 (0.14)	3.66 (0.17)
Placebo + CST; targeted	—	4.93 (0.22)	4.81 (0.24)	4.08 (0.18)	4.06 (0.20)	3.96 (0.20)	3.57 (0.18)

Summary of number of drinks per day in females

Interventions	Mean (SEM)						
	Baseline	2 wks	4 wks	6 wks	8 wks	10 wks	12 wks
Naltrexone + CST; daily	—	2.84 (0.21)	3.71 (0.29)	3.42 (0.25)	3.01 (0.18)	3.33 (0.35)	3.21 (0.27)
Naltrexone + CST; targeted	—	2.96 (0.19)	3.02 (0.19)	2.70 (0.17)	2.82 (0.20)	2.84 (0.18)	2.96 (0.24)
Placebo + CST; daily	—	3.74 (0.23)	3.43 (0.21)	3.13 (0.21)	2.63 (0.24)	2.67 (0.26)	2.40 (0.26)
Placebo + CST; targeted	—	3.49 (0.23)	3.25 (0.21)	3.06 (0.21)	3.10 (0.25)	3.23 (0.29)	2.78 (0.20)

Reference; study design; study outcomes reported; relevant drinking outcomes	Relevant drinking outcomes: study results and conclusions
	Daily naltrexone was observed not to be better than placebo in terms of reducing 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). **Study Conclusions** For a comparative assessment of naltrexone versus nalmefene, the results reported were converted, and a weighted average was calculated using: • The data at every time point • The proportion of males at baseline of 58.3% • The intent-to-treat number of patient by treatment arm at baseline • 1 drink = 14 grams (US conversion) The results show the highest difference between naltrexone and nalmefene at week 2, and that naltrexone is not better than placebo at the end of the study. **Follow-up time** / **Difference placebo – naltrexone (g/day)** 2 weeks: 6.96 4 weeks: 2.58 6 weeks: −1.86 8 weeks: 0.22 10 weeks: 1.31 12 weeks: 0.01 These results are aligned with authors' conclusion when comparing the most effective treatment with the combination of the three others: 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

Reference; study design; study outcomes reported; relevant drinking outcomes	Relevant drinking outcomes: study results and conclusions
	significant (multilevel regression results: b = −0.18, SE = 0.13, *P* = 0.15). **Conclusion:** This study has not demonstrated a higher efficacy of naltrexone versus placebo in reduction.
Hernandez-Avila et al. (2006) presents a secondary analysis of data from Kranzler et al. (2003). Kranzler et al. (2009) reports an extension of the study reported by Kranzler et al. (2003). CBT = cognitive behavioural therapy; CST = coping skills therapy; SEM = standard error of the mean; SBT = supportive behavioural therapy; SD = standard deviation.	

Systematic review for psychosocial intervention studies

In order to perform an indirect comparison of identified psychosocial interventions versus BRENDA when used in the context of the pivotal nalmefene + BRENDA studies (i.e., in actively drinking alcohol-dependent patients with a treatment goal of reducing consumption), the following drinking outcomes of relevance were considered:

- Level of alcohol consumption
- Number of drinks/day
- Number of HDDs
- Percent HDDs

Thus, the outcomes of relevance in the psychosocial intervention studies were the same as in the naltrexone studies.

The following drinking outcomes were not of relevance and were not considered:

- Number of drinks per drinking day
- Number of drinking days
- Percent drinking days
- Time to first HDD
- Proportion of patients who return to heavy drinking

The PI studies identified in the updated systematic literature review are summarised in Section 10.6, Appendix 6, along with the relevant studies from the original NICE CG115 systematic review of PI studies.

Table B28 summarises the 50 identified psychosocial intervention studies, 43 from the original NICE review and 7 from the updated review conducted by Lundbeck, summarising the range of change from baseline to end of follow-up for relevant drinking outcomes.

Table B28. Summary of identified psychosocial interventions trials: study design and outcomes

Psychosocial intervention	Comparisons	Included studies by NICE CG 115	Treatment types from included studies by NICE CG 115	Included studies from Lundbeck update of the NICE CG 115 review	Treatment types from included studies by Lundbeck update of the NICE CG 115 review	Range of change from baseline to end of follow-up for relevant drinking outcomes comparable to nalmefene trial outcomes[a]
Motivational techniques	Motivational vs. control; Motivational vs. other intervention	Davidson 2007; Hester 2005; Match 1997; Rosenblum 2005; Sellman 2001; Shakeshaft 2002; Sobell 2002; UKATT 2005	• Motivational Techniques:- motivational enhancement therapy with/without relapse prevention, drinker's check-up, FRAMES (feedback, responsibility, advice, menu, empathy, self-efficacy) • Other:- broad spectrum treatment, CBT, TSF, non-directive reflective listening (counselling) • Control:- wait list control, information and referral, feedback	Brown et al., 2007; Field et al., 2010; Weinreb et al., 2011	None	TAC (g/day) • Range of follow-up time: 6 months - 12 months • Range of change from baseline: 9.3 g/day – 50.7 g/day • Median value: 18.3g/day No. of HDD per month • Range of follow-up time: 3 months – 12 months • Range of change from baseline: 1.3 HDD – 19 HDD • Median value: 5.7 HDD
Cognitive behavioural therapies	Cognitive Behavioural vs. TAU; Cognitive Behavioural vs. other intervention; different formats of cognitive behavioural therapies	Burtscheidt 2002; Marques 2001; Connors 2001; Davidson 2007; Easton 2007; Eriksen 1986; Lam 2009; Litt 2003; Litt 2009; MATCH 1997; Monti 1990; Monti 1993; Morgenstern 2007; Rosenblum 2005a, Rosenblum 2005b; Sandahl 1998; Shakeshaft 2002; Sitharthan 1997;	• Cognitive behavioural therapy:- individual CBT with/without relapse prevention or MET, alcohol-focused coping skills, group CBT, broad spectrum treatment, group social skills training, communication skills training with/without family therapy, cognitive behavioural mood management training, coping skills with/without cue exposure or MET,	Sobell et al., 2009; Walitzer et al., 2009; Wiers et al., 2011	Cognitive behavioural therapy:- GSC (guided self-change (a type of cognitive behavioural motivational intervention)- individual treatment vs. GSC group treatment	TAC (g/day) • Range of follow-up time: 6 months - 15 months • Range of change from baseline: 9.3 g/day – 159.04 g/day • Median value: 52.13g/day No. of HDD per month • Range of follow-up time: 3 months - 15 months

Psychosocial intervention	Comparisons	Included studies by NICE CG 115	Treatment types from included studies by NICE CG 115	Included studies from Lundbeck update of the NICE CG 115 review	Treatment types from included studies by Lundbeck update of the NICE CG 115 review	Range of change from baseline to end of follow-up for relevant drinking outcomes comparable to nalmefene trial outcomes[a]
		Vedel 2008; Walitzer 2009	relapse prevention with MET • Other:- MET, TSF with/without coping skills, counselling, BCT, psychodynamic therapy, cue exposure, FRAMES • Control:- non-specific supportive therapy, TAU with a daily craving record, Information and referral			• Range of change from baseline: 1.3 HDD – 19 HDD • Median value: 7.04 HDD
Behavioural therapies	Behavioural vs. TAU or control; Behavioural vs. other intervention; different formats of behavioural therapy	Alden 1988; Heather 2000; Kavanagh 2006; Monti 1993; Sitharthan 1997; Walitzer 2004	• Behavioural:- BSMT/ BSCT, moderation-oriented cue exposure, cue exposure with CBT, emotional cue exposure with CBT, cue exposure with coping skills • Other:-developmental counselling, CBT, behavioural couples therapy, alcohol focused spousal involvement • Control:- wait list control, treatment as usual	Jung et al., 2011;	None	TAC (g/day) • Range of follow-up time: 6 months – 12 months • Range of change from baseline: 2.9 g/day – 182 g/day • Median value: 20.75 No. of HDD per month • Range of follow-up time: 6 months - 12 months • Range of change from baseline: 0.9 HDD – 13 HDD • Median value: 2.3 HDD

Psychosocial intervention	Comparisons	Included studies by NICE CG 115	Treatment types from included studies by NICE CG 115	Included studies from Lundbeck update of the NICE CG 115 review	Treatment types from included studies by Lundbeck update of the NICE CG 115 review	Range of change from baseline to end of follow-up for relevant drinking outcomes comparable to nalmefene trial outcomes[a]
Social network and environment based therapies	Soc/Net Therapy vs. control; Soc/Net Therapy vs. other intervention	Leigh 1999; Litt 2007; UKATT 2005	• Soc/Net therapy:- volunteer support, network support with/without contingency management, social behaviour and network therapy • Other: Office based intervention (no direct support), motivational enhancement therapy • Control:- Case management	NA	NA	TAC (g/day) • Range of follow-up time: 12 months - 12 months • Range of change from baseline: 122.4 g/day – 129.2 g/day • Median value: 125.8 No. of HDD per month • Range of follow-up time: NR • Range of change from baseline: NR • Median value: NR
Contingency management (CM)	CM vs. control; CM vs. TAU; CM vs. other intervention	Alessi 2007, Litt 2007, Petry 2000	• CM:- CM plus standard treatment or network support • Other:- Network support • Control: Standard treatment, case management	NA	NA	TAC (g/day) • Range of follow-up time: NR • Range of change from baseline: NR • Median value: NR No. of HDD per month • Range of follow-up time: NR • Range of change from baseline: NR • Median value: NR

[a] Studies in the inpatient setting were excluded, as nalmefene is indicated for the outpatient setting.

BCT= behavioural couples therapy; BSMT= behavioural self-management training; CBT= cognitive behavioural therapy; CM=contingency management; FRAMES= feedback, responsibility, advice, menu, empathy, self-efficacy; GSC=guided self-change; HDD= heavy drinking days; MET= motivational enhancement therapy; NA = not applicable; TAC= total alcohol consumption; TAU= treatment as usual; TSF= twelve step facilitation

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

Systematic review for naltrexone

Table B29 summarises the limitations and feasibility assessment for indirect comparison of the naltrexone studies with the nalmefene studies. As shown in the table, all identified studies had limitations in reporting of data (not reporting values for TAC, not reporting drinking levels at baseline, lack of reported data for the drinking outcomes, and not reporting the evaluable number of patients) that meant that an indirect meta-analysis could not be conducted in line with NICE recommendations for evidence synthesis for decision making (NICE, 2011b). Therefore, inclusion of a comparison of nalmefene versus naltrexone in line with the NICE reference case was not possible.

Table B29. Summary of identified naltrexone trials: limitations and feasibility assessment for indirect comparison with nalmefene

References of trials	Limitations and feasibility assessment for indirect comparison with nalmefene
Heinälä et al., 2001	There was selective reporting of data in terms of providing final values for total alcohol consumption, with no mention of drinking levels at baseline. This selective reporting of data allowed an incomplete assessment of the population included in the study and limits the development of an indirect meta-analysis versus nalmefene.
Kranzler et al., 2003 Hernandez-Avila et al., 2006	This was a pilot study of short duration conducted on a small proportion of patients. The study lacked reported 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. This led to exclusion of the study for indirect meta-analysis versus nalmefene.
Kranzler et al., 2009	This was a pilot study of short duration conducted on a small proportion of patients. A graphical representation of data was provided for the relevant drinking outcomes. Data for these outcomes were extracted from the graphs using Engauge Digitizer 4.1 software. However, the data could not be used for indirect meta-analysis with nalmefene because: • baseline drinking level data for the reported subgroups were not reported • the evaluable number of patients for the reported subgroups were not reported

Systematic review for psychosocial comparators

From the original and updated PI systematic literature review, and mainly because there is no common treatment arm to be used in conjunction with the nalmefene clinical trials, an indirect meta-analysis could not be conducted in line with NICE recommendations for evidence synthesis for decision-making (NICE, 2011b). In addition to data availability, other considerations that limit the value of assessing these studies with regard to the nalmefene studies include the assessed population of patients and the applicability of these studies in the UK context. Indeed, only two studies have been conducted in

the UK: UKATT 2005 compared Social Behaviour & Network Therapy (SBNT) and Motivational Enhancement Therapy (MET), and Heather 2000 compared Moderation-Oriented Cue Exposure (MOCE) and Behavioural Self-Control Training (BSCT). Unfortunately, none of these studies provided an endpoint of relevance to be used in comparative assessment versus the outcomes from the nalmefene RCTs.

Table B30 presents a summary of the results of absolute reductions in drinking results from the PI studies from the original and updated PI systematic literature review. Results from the pivotal nalmefene trials are also presented in this table.

These results are of very limited use considering the appropriate approach of indirect meta-analysis guided by NICE, but may guide the following qualitative assessment: the PI most aligned as a proxy of the psychosocial support recommended with the use of nalmefene is motivational techniques. As shown in Table B28, the absolute reduction in TAC (g/day) from these studies range from 9.3 g/day to 50.7 g/day, with a median value of 18.3 g/day (range of follow-up time: 6 months to 12 months). For the number of HDDs per month, the range was from 1.3 HDD to 19 HDD, with a median value of 5.7 HDD (range of follow-up time: 3 months to 12 months). Looking at nalmefene trials results, the range in absolute reduction of TAC was from 58.3 to 70.4 for nalmefene + PI; from 40 to 49.8 for placebo + PI; and the range in absolute reduction of monthly HDD was from 11.6 to 12.9 for nalmefene + PI; from 8 to 8.6 for placebo + PI (Table B30). These findings may lead to the observation that the placebo effect has reduced the relative effect of nalmefene + PI versus PI alone in the RCT context, and that this differential effect is most likely to be higher in real-life practice. Nevertheless, a variation of the effect of PI alone has been taken into account in the cost-effectiveness sensitivity analysis for providing a threshold analysis of varying the effect of PI alone.

Table B30. Summary of results on absolute reduction in drinking reported in the psychosocial intervention trials

Reference (PI)	Change from baseline in TAC, g/day [mean]	Change from baseline in HDDs/month
Motivational Techniques		
Davidson 2007 (BST)	N/A	12.7
Davidson 2007 (MET)	N/A	13
Hester 2005 (DCU)	50.7	N/A
Hester 2005 (Control)	43.96	N/A
Rosenblum 2005b (RPME [MET] [Baseline 1-15 HDD])	N/A	5.9
Rosenblum 2005b (Control [Baseline 1-15 HDD])	N/A	1.3
Rosenblum 2005b (RPME [MET] [Baseline 16-30 HDD])	N/A	19
Rosenblum 2005b (Control [Baseline 16-30 HDD])	N/A	4.11
Shakeshaft 2002 (FRAMES)	11.1	7.8
Shakeshaft 2002 (CBT)	9.3	5.5
Sobell 2002 (MET)	19.4	4.75
Sobell 2002 (PSYEDU)	17.2	4.13
Cognitive Behavioural Therapies		
Marques 2001 (GR CBT)	34.3	6.7
Marques 2001 (IND CBT)	25.7	6
Davidson 2007 (BST)	N/A	12.7
Davidson 2008 (MET)	N/A	13
Litt 2009 (PCBT)	N/A	11.2
Litt 2010 (IATP)	N/A	12.9
Monti 1990 (CST)	141.68	10.12
Monti 1991 (CSTF)	159.04	11.36
Monti 1992 (CBMMT)	71.96	5.14
Monti 1993 (CE+CS [CBT])	182	13
Monti 1994 (TAU)	84	6
Morgenstern 2007 (MI + CBT)	56.84	N/A
Morgenstern 2007 (MI)	48.58	N/A
Rosenblum 2005b (RPME [Baseline 1-15 HDD])	N/A	5.9
Rosenblum 2005b (Control [Baseline 1-15 HDD])	N/A	1.3
Rosenblum 2005b (RPME [Baseline 16-30 HDD])	N/A	19
Rosenblum 2005b (Control [Baseline 16-30 HDD])	N/A	4.11
Sandahl 1998 (RP)	N/A	6.7
Sandahl 1998 (PSYDY)	N/A	6.7
Shakeshaft 2002 (FRAMES)	11.1	7.8
Shakeshaft 2002 (CBT)	9.3	5.5
Sobell 2009 (Group GSC)	N/A	6.57
Sobell 2009 (Individual GSC)	N/A	7.38
Vedel 2008 (CBT)	52.13	N/A

Reference (PI)	Change from baseline in TAC, g/day [mean]	Change from baseline in HDDs/month
Vedel 2008 (BCT)	50.21	N/A
Walitzer 2009 (CS)	N/A	5.88
Walitzer 2009 (DIR+CS)	N/A	7.28
Walitzer 2009 (MOT+CS)	N/A	5.88
Behavioural Therapies		
Alden 1998 (BSMT)	41.75	N/A
Alden 1998 (Counselling)	48.79	N/A
Kavanagh 2006 (CBT [men])	22.9	N/A
Kavanagh 2007 (CBT [women])	10	N/A
Kavanagh 2008 (CE [men])	18.6	N/A
Kavanagh 2009 (CE [women])	2.9	N/A
Kavanagh 2010 (ECE [men])	5.7	N/A
Kavanagh 2011 (ECE [women])	8.6	N/A
Monti 1993 (CE+CS [CBT])	182	13
Monti 1993 (TAU)	84	6
Walitzer 2004 (BSM)	N/A	0.9
Walitzer 2004 (AFSI)	N/A	1.7
Walitzer 2004 (BCT)	N/A	2.3
Social Network and Environment Based Therapies		
Leigh 1999 (OB)	122.4	N/A
Leigh 1999 (VS)	129.2	N/A
Pivotal Nalmefene Studies		
ESENSE 1 (Nalmefene + PI)	58.3	11.6
ESENSE 1 (Placebo + PI)	40	8
ESENSE 2 (Nalmefene + PI)	70.4	12.9
ESENSE 2 (Placebo + PI)	60.1	10.2
SENSE (Nalmefene + PI)	67.1	12.2
SENSE (Placebo+ PI)	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

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

See Section 6.7.4.

6.7.6 Please present the results of the analysis.

See Section 6.7.4.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

See Section 6.7.4.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

See Section 6.7.4.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

See Section 6.7.4.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's "Guide to the methods of technology appraisal," Sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see Section 6.2.7), please repeat the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in "Systematic reviews: CRD's guidance for undertaking reviews in healthcare" (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in Sections 10.6 and 10.7, Appendices 6 and 7.

The systematic review identified no relevant nalmefene non-RCT articles.

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from noncomparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in Sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in "Systematic reviews: CRD's guidance for undertaking reviews in healthcare" (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in Sections 10.8 and 10.9, Appendices 8 and 9.

SENSE (12013A) was a 52-week study to evaluate the long-term safety and tolerability of as-needed nalmefene with a protocol amendment to include efficacy analyses. SENSE was a predefined safety study with no power calculations undertaken on efficacy outcomes prior to the commencement of the study; SENSE had a trial design that reflected a primary safety study (3:1 randomisation).

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

An integrated safety database, including data from the placebo and nalmefene groups from ESENSE1, ESENSE2, and SENSE, was created, and a pooled data set was prepared to allow for comparison of safety data across treatment groups. The analyses of safety and tolerability were based on the all-patients-treated set (APTS), which comprised all patients excluding those with no recorded investigational medicinal product intake and all investigational medicinal product returned. Safety results are presented first for the total trial population and then for the licensed population.

Adverse events

Total population

Frequent adverse events were defined as treatment-emergent adverse events with an incidence ≥ 5% in either treatment group (Table B31). The most common adverse events associated with nalmefene were related to the central nervous system and the gastrointestinal system, reflecting antagonism at the opioid receptors. Adverse events observed with the highest incidences in the nalmefene group as compared with the placebo group were nausea, dizziness, insomnia, and headache.

Table B31. Treatment-emergent AEs with an incidence of ≥ 5% in either treatment group: total population

Preferred Term	Nalmefene + PI (n = 1,144)	Placebo + PI (n = 797)
Patients with treatment-emergent AEs, n (%)	855 (74.7)	500 (62.7)
Nausea, n (%)	253 (22.1)	47 (5.9)
Dizziness, n (%)	208 (18.2)	44 (5.5)
Insomnia, n (%)	153 (13.4)	43 (5.4)
Headache, n (%)	141 (12.3)	66 (8.3)
Nasopharyngitis, n (%)	107 (9.4)	73 (9.2)
Vomiting, n (%)	100 (8.7)	18 (2.3)
Fatigue, n (%)	95 (8.3)	37 (4.6)
Somnolence, n (%)	59 (5.2)	23 (2.9)

AE = adverse event; PI = psychosocial intervention.

Source: Lundbeck, 2012e.

Licensed population

The overall incidences and pattern of adverse events were not substantially different for patients with a high/very high DRL at baseline and randomisation than for the total population (Table B32).

Table B32. Treatment-emergent AEs with an incidence of ≥ 5% in either treatment group in patients with a high/very high DRL at baseline and randomisation: licensed population

AE	Nalmefene + PI (n = 475)	Placebo + PI (n = 369)
Patients with treatment-emergent AEs, n (%)	368 (77.5)	246 (66.7)
Nausea, n (%)	115 (24.2)	24 (6.5)
Dizziness, n (%)	104 (21.9)	22 (6.0)
Insomnia, n (%)	69 (14.5)	16 (4.3)
Headache, n (%)	60 (12.6)	35 (9.5)
Fatigue, n (%)	43 (9.1)	22 (6.0)
Vomiting, n (%)	40 (8.4)	13 (3.5)
Nasopharyngitis, n (%)	38 (8.0)	39 (10.6)
Sleep disorder, n (%)	32 (6.7)	4 (1.1)
Hyperhidrosis, n (%)	28 (5.9)	3 (0.8)
Decreased appetite, n (%)	27 (5.7)	4 (1.1)
Diarrhoea, n (%)	19 (4.0)	22 (6.0)
Accidental overdose, n (%)	13 (2.7)	22 (6.0)

AE = adverse event; DRL = drinking risk level; PI = psychosocial intervention.

Source: Lundbeck, 2012e.

Onset and duration of adverse events

Total population

Frequent adverse events were of short duration, lasting from 1 day (vomiting) to 7 days (nasopharyngitis) in patients treated with nalmefene (Table B33).

Table B33. Duration of frequent AEs: total population

AE	Nalmefene + PI (median, days)	Placebo + PI (median, days)
Nausea	3.0	3.0
Dizziness	3.0	2.5
Insomnia	5.0	8.0
Headache	2.0	3.0
Nasopharyngitis	7.0	10.0
Vomiting	1.0	2.0
Fatigue	7.0	20.0
Somnolence	2.0	10.0

AE = adverse event; PI = psychosocial intervention.

Source: Lundbeck, 2012e.

The overall pattern of nasopharyngitis (most commonly reported as common cold) in the nalmefene group was similar to that in the placebo group. For the other frequent adverse events, the overall pattern in the nalmefene group was that of mild or moderate adverse events related to nalmefene (e.g., fatigue and somnolence) and was similar or shorter in duration than in the placebo group.

In the nalmefene group, onset of frequent adverse events occurred within the first 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 (the median duration was ≤ 7 days for all the frequent adverse events in the nalmefene group).

Central nervous system and gastrointestinal events (nausea, dizziness, insomnia, headache, vomiting, fatigue, and somnolence), which had higher incidences in the nalmefene group than in the placebo group reflected antagonism at the opioid receptors.

Licensed population

For the licensed population (patients with a high/very high DRL at baseline and randomisation), the overall pattern of adverse events was similar to those in the total population (Table B34).

Table B34. Duration of frequent AEs in high/very high DRL at baseline and randomisation: licensed population

AE	Nalmefene + PI (median, days)	Placebo + PI (median, days)
Nausea	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]

AE = adverse event; DRL = drinking risk level; PI = psychosocial intervention.

Source: Lundbeck, 2012e.

[redacted]

In the nalmefene group, onset of frequent adverse events occurred within the first 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 (the median duration was ≤ 7 days for all the frequent adverse events in the nalmefene group).

As in the total population, central nervous system and gastrointestinal events in the licensed population (nausea, dizziness, insomnia, headache, vomiting,

fatigue, and somnolence), which had higher incidences in the nalmefene group than in the placebo group, reflected antagonism at the opioid receptors.

Adverse events leading to withdrawal

Total population

A total of 47 patients (6%) in the placebo group and 149 patients (13%) in the nalmefene group withdrew due to treatment-emergent adverse events. The treatment-emergent adverse events leading to withdrawal with an incidence ≥ 1% all occurred in the nalmefene group and were dizziness, nausea, fatigue, and headache (Table B35).

Table B35. AEs with an incidence of ≥ 0.5% in either treatment group leading to withdrawal: total population

Reasons for withdrawal, n (%)	Nalmefene + PI (n = 1,144)	Placebo + PI (n = 797)
Patients with treatment-emergent AEs leading to withdrawal	149 (13.0)	47 (5.9)
Dizziness	36 (3.1)	0 (0.0)
Nausea	30 (2.6)	0 (0.0)
Fatigue	15 (1.3)	0 (0.0)
Headache	13 (1.1)	0 (0.0)
Insomnia	10 (0.9)	2 (0.3)
Vomiting	9 (0.8)	1 (0.1)
Hyperhidrosis	8 (0.7)	0 (0.0)
Alcohol withdrawal syndrome	7 (0.6)	3 (0.4)
Disturbance in attention	7 (0.6)	0 (0.0)
Depression	5 (0.4)	7 (0.9)

AE = adverse event; PI = psychosocial intervention.

Source: Lundbeck, 2012e.

Licensed population

The overall pattern of treatment-emergent adverse events leading to withdrawal in the licensed population (patients with a high/very high DRL at baseline and randomisation) was similar to that in the total population (Table B36).

Table B36. AEs with an incidence of ≥ 0.5% in the nalmefene treatment group leading to withdrawal in patients with high/very high DRL at baseline and randomisation: licensed population

Reasons for withdrawal, n (%)	Nalmefene + PI (N = 475)	Placebo + PI (N = 369)
Patients with treatment-emergent AEs leading to withdrawal	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Hyperhidrosis	[redacted]	[redacted]
Sleep disorder	[redacted]	[redacted]
Disorientation	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Alcohol withdrawal syndrome	[redacted]	[redacted]
Disturbance in attention	[redacted]	[redacted]
Feeling abnormal	[redacted]	[redacted]

AE = adverse event; DRL = drinking risk level; PI = psychosocial intervention.

Source: Lundbeck, 2012e.

[redacted]

Serious adverse events

Total population

A total of 35 patients (4.4%) in the placebo group and 57 patients (5.0%) in the nalmefene group had serious adverse events (SAEs). Most SAEs were considered not related to the investigational medicinal product. There were no apparent trends in the SAEs with respect to overall incidence or distribution across preferred terms, except that fewer patients had alcohol withdrawal syndrome in the placebo group (1 patient [0.1%]) than in the nalmefene group (8 patients [0.7%]).

Table B37 summarises SAEs (preferred term) that occurred in more than 1 patient in either treatment group.

Table B37. SAEs in > 1 patient in either treatment group: total population

SAE preferred term, n (%)	Nalmefene + PI (n = 1,144)	Placebo + PI (n = 797)
Total number of patients with treatment-emergent SAEs	57 (5.0)	35 (4.4)
Alcohol withdrawal syndrome	8 (0.7)	1 (0.1)
Alcoholism	4 (0.3)	2 (0.3)
Fall	3 (0.3)	1 (0.1)
Alcohol poisoning	2 (0.2)	2 (0.3)
Atrial fibrillation	2 (0.2)	0 (0.0)
Depression	2 (0.2)	0 (0.0)
Disorientation	2 (0.2)	0 (0.0)
Noncardiac chest pain	2 (0.2)	0 (0.0)
Alcohol abuse	1 (0.1)	2 (0.3)
Fibula fracture	1 (0.1)	2 (0.3)
Pneumonia	1 (0.1)	2 (0.3)
Completed suicide	0 (0.0)	2 (0.3)
Convulsion	0 (0.0)	2 (0.3)
Hypertension	0 (0.0)	2 (0.3)
Intentional overdose	0 (0.0)	2 (0.3)
Pneumothorax	0 (0.0)	2 (0.3)
Pyothorax	0 (0.0)	2 (0.3)
Rib fracture	0 (0.0)	2 (0.3)
Tibia fracture	0 (0.0)	2 (0.3)

PI = psychosocial intervention; SAE = serious adverse event.

Source: Lundbeck, 2012e.

Licensed population

The overall pattern of SAEs in the licensed population (patients with a high/very high DRL at baseline and randomisation) was similar to that in the total population (Table B38).

Table B38. SAEs in > 1 patient in either treatment group in patients with high/very high DRL at baseline and randomisation: licensed population

SAE preferred term, n (%)	Nalmefene + PI (n = 475)	Placebo + PI (n = 369)
Total number of patients with treatment-emergent SAEs	26 (5.5)	13 (3.5)
Alcoholism	2 (0.4)	1 (0.3)
Fall	2 (0.4)	1 (0.3)
Noncardiac chest pain	2 (0.4)	0 (0.0)
Pneumothorax	0 (0.0)	2 (0.5)
Rib fracture	0 (0.0)	2 (0.5)

DRL = drinking risk level; PI = psychosocial intervention; SAE = serious adverse event.

Source: Lundbeck, 2012e.

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

In the ESENSE1, ESENSE2, and SENSE studies, nalmefene demonstrated a favourable risk-benefit balance for patients with high/very high DRL at baseline and randomisation (EMA, 2012).

The safety profile of nalmefene in ESENSE1, ESENSE2 and SENSE indicated that most of the adverse events observed with nalmefene were associated with treatment initiation. These were generally mild or moderate in severity and appeared for a short duration. The most common adverse events associated with nalmefene were related to the central nervous system and the gastrointestinal system, reflecting antagonism at the opioid receptors. Adverse events observed with the highest incidences in the nalmefene group as compared with the placebo group were nausea, dizziness, insomnia, and headache. The overall incidence and pattern of adverse events were not substantially different for patients in the licensed population compared with the total trial population.

There were no unexpected withdrawals across the treatment groups in ESENSE1, ESENSE2, and SENSE. When data were pooled for all three nalmefene studies, it was observed that the proportions of patients who withdrew from the studies due to adverse events were greater in the nalmefene groups than in the placebo groups (13% in the nalmefene group and 6% in the placebo group). The adverse events leading to withdrawal in ≥ 1% of the patients in the nalmefene group were dizziness, nausea, fatigue, and headache. The overall incidence of withdrawal and of withdrawal due to adverse events were similar for the licensed population (patients with a high/very high DRL at baseline and randomisation) and for the total population.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Nalmefene's efficacy and tolerability in patients with alcohol dependence has been demonstrated in two 6-month studies (ESENSE1 and ESENSE2) and one 12-month study (SENSE), highlighting the robustness of the results. Results from the ESENSE1, ESENSE2, and SENSE trials show that nalmefene + PI is more effective than placebo + PI at reducing the number of HDDs and TAC in patients with alcohol dependence.

- In ESENSE1 and ESENSE2, nalmefene reduced the number of HDDs significantly more than placebo from baseline to month 6. In both studies, the effect in favour of nalmefene was observed by month 1 and maintained throughout the study period.

- Nalmefene was significantly superior to placebo in reducing TAC at all time points measured from month 1 to month 6 in both ESENSE1 and ESENSE2.

- In the SENSE study, nalmefene reduced the number of HDDs and TAC consistently more than placebo throughout the 1-year treatment period in the licensed population. The difference in treatment effect between nalmefene and placebo persisted throughout the treatment period and even increased with time, indicating that tolerance to the effectiveness of nalmefene does not develop within at least 12 months of treatment.

In all three studies (ESENSE1, ESENSE2, and SENSE), the patients with a high/very high DRL at baseline and randomisation (licensed population) derived a greater benefit from nalmefene treatment than observed in the total population. Furthermore, treatment with nalmefene consistently led to clinically meaningful improvements as shown by the responder analyses.

In patients with a high/very high DRL at baseline and randomisation, a greater improvement in GGT and ALAT were observed in the nalmefene group at month 6 in both ESENSE1 and ESENSE2 compared with the placebo group. The difference was in favour ($P < 0.05$) of nalmefene for both GGT and ALAT in ESENSE1 and for ALAT in ESENSE2. The EMA guideline on the development of medicinal products for the treatment of alcohol dependence recommends that a combination of biomarkers should be measured at baseline and followed during the course of treatment as secondary outcome variables to monitor the effect of treatment (EMA, 2010). These validated biomarkers (ALAT and GGT) are a reflection of hepatic damage and provide objective outcome measures to support drinking and responder measures.

The SENSE study provided evidence of the efficacy of nalmefene up to 1 year of treatment. The high retention rate observed in the study (62% of the patients in the total population completed the study) indicated that, for most patients, nalmefene was well accepted over an extended period.

Improvements were observed in HRQL with nalmefene compared with placebo, as measured by the mental and physical component scores of the SF-36, by the EQ-5D health state score and utility index score, and by the DrInC in the pooled ESENSE1 and ESENSE2 studies.

Most adverse events observed with nalmefene were associated with treatment initiation. These were generally mild or moderate in severity and appeared for a short duration. Adverse events observed with the highest incidences in the nalmefene group as compared with the placebo group were nausea, dizziness, insomnia, and headache. The overall incidences and pattern of adverse events were not substantially different for patients with a high/very high DRL at baseline and randomisation than for the total population.

Confusional state and, rarely, hallucinations and dissociation were reported in the clinical studies. Most of these reactions were mild or moderate, associated with treatment initiation, and of short duration (a few hours to a few days). Most of these adverse reactions resolved during continued treatment and did not recur upon repeated administration. Although these events were generally short-lasting, they could represent alcoholic psychosis, alcohol withdrawal syndrome, or comorbid psychiatric disease (Nalmefene SPC, 2013).

During the nalmefene clinical trials, adherence to the as-needed dosing regimen was defined as a day when there was alcohol consumption and concomitant nalmefene medication intake or a day when there was no alcohol consumption. Based on this definition, pooling ESENSE1, ESENSE2, and SENSE, in the licensed population, the concept of as-needed dosing engaged the patients in active and responsible management of their illness and was well understood and followed by patients in the placebo and nalmefene treatment arms. In nalmefene-treated patients, 82% adherence was seen in the licensed population (Table B39).

Table B39. Adherence to medication in the total population and among patients with high/very high DRL at baseline and randomisation (pooled data from ESENSE1, ESENSE2, and SENSE)

			Adherence, mean %			Non-adherence, mean %
	Intervention	**N**	**IMP intake and drinking**	**IMP intake and no drinking**	**No IMP intake and no drinking**	**No IMP intake and drinking**
Total population	PBO + PI	789	41.2	20.9	27.4	10.4
	NMF + PI	1,134	31.6	19.1	36.4	12.7
Licensed population	PBO + PI	365	57.1	14.0	16.5	12.4
	NMF + PI	470	42.8	12.9	25.9	17.9

DRL = drinking risk level; IMP = investigational medicinal product; NMF = nalmefene; PBO = placebo; PI = psychosocial intervention.

In the licensed population, patients took investigational medicinal product (IMP) an average of 56% and 71% of the days for nalmefene and placebo groups, respectively (Table B40). Additionally, IMP intake decreased slowly during the treatment period in the licensed population; during the first month, the patients in the nalmefene and placebo groups took IMP on 66% and 77% of the days, respectively, which by the sixth month had decreased slightly to 57% and 70%, respectively. During the last month of SENSE, the patients took IMP on 46% and 56% of the days in the nalmefene and placebo groups, respectively. Thus, over 12 months, nalmefene intake was reduced by approximately 20%. Furthermore, nalmefene drug intake reduced with reduced level of alcohol consumption. Table B41 details the average monthly nalmefene intake for males and females per drinking level category, pooling data from the three nalmefene trials; these data are used in the cost-effectiveness model presented in Section 7.

Table B40. IMP intake of the licensed population (high or very high DRL) (APTS)

		ESENSE1	ESENSE2	SENSE	Pooled (3 studies)
IMP intake (% of days)	Nalmefene + PI	51%	65%	52%	56%
IMP intake (% of days)	Placebo + PI	73%	71%	62%	71%

APTS = all-patients-treated set; DRL = drinking risk level; IMP = investigational medicinal product; PI = psychosocial intervention

Table B41. Nalmefene dose intake per drinking level in pooled ESENSE1, ESENSE2, and SENSE pooled: licensed population

Drinking level	Average intake per month (28 days)	
	Males	Females
Very high risk	20.5	19.1
High risk	19.9	18.9
Medium risk	16.5	16.5
Low risk	13.9	14.8
Abstinence	8.8	7.7

The above demonstrates the therapeutic advantage and efficacy of as-needed nalmefene dosing, including high adherence and the reduction of nalmefene intake when alcohol consumption reduces, which also avoids unnecessary exposure to treatment and related potential side effects.

The results in Table B39 and Table B41 demonstrate the therapeutic advantage of as-needed dosing with the high adherence to nalmefene as-needed regimen; and also with the fact that the dose intake of nalmefene reduces when reduced alcohol consumption – as aligned with nalmefene demonstrated efficacy – and this constitutes an illustration of the efficacy of

the as-needed care in alcohol dependence; in addition to avoid unnecessary exposure to treatment and related potential side effects.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths

The Lundbeck-sponsored phase 3 programme for nalmefene enrolled 1,997 alcohol-dependent patients across Europe. All three studies (ESENSE1, ESENSE2, and SENSE) were conducted in different regions in Europe to ensure that different drinking cultures were represented. Thus, the results are very relevant to a European population.

All three studies were randomised, double-blinded, placebo-controlled, parallel-group studies assessing as-needed nalmefene for the reduction of alcohol consumption in patients with alcohol dependence diagnosed according to DSM-IV. The phase 3 programme gave consistent results demonstrating the efficacy of nalmefene, especially when emphasis was placed on patients with a high/very high DRL (as recommended by the EMA); these patients have a greater unmet medical need for treatment (EMA, 2010).

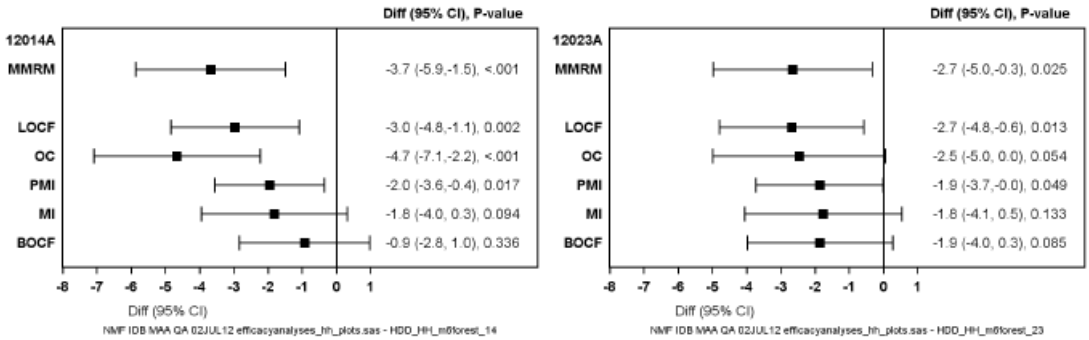
All the nalmefene trials fulfilled the requirements of the EMA guidelines for development of products to reduce alcohol consumption with subsequent harm reduction (EMA, 2010). According to the EMA guidelines, if a study drug addresses the goal of clinically significant moderation, efficacy should be expressed by change from baseline in TAC (per month, presented as amount of pure alcohol in grams per day) as well as by reduction in the number of HDDs (defined as ≥ 60 g/day of pure alcohol in men and ≥ 40 g/day of pure alcohol in women). As per the EMA recommendations for harm reduction studies, the nalmefene trials conducted by Lundbeck had adequate length of study duration, adequate selection and assessment of outcomes (both primary and secondary outcomes), and analysis of the right patient population (with high/very high DRL at baseline and randomisation).

Although the 1-year study (SENSE) was primarily designed as a safety study, secondary efficacy outcomes demonstrated that the difference in treatment effect between nalmefene and placebo persisted throughout the treatment period and even increased with time, which indicated that tolerance to the effect of nalmefene did not develop with at least 12 months of treatment. In addition, nalmefene had a well-described safety and tolerability profile.

Several sensitivity analyses on imputation methods were performed to evaluate how different assumptions would influence the estimates of the treatment effect (Figure B15 and Figure B16). These analyses provided further reassurance of the clinical effects of nalmefene. Mixed model repeated measures results showed the response from the perspective of efficacy for patients adhering to treatment. The set of sensitivity analyses showed that a statistically significant difference was demonstrated, as the analyses were regarded as conservative response estimates. All the sensitivity analyses

were in favour of nalmefene, irrespective of the imputation method (EMA, 2012).

Figure B15. Sensitivity analyses: change from baseline to month 6 in HDDs (FAS) in patients with a high/very high DRL at baseline and randomisation (ESENSE1 and ESENSE2)

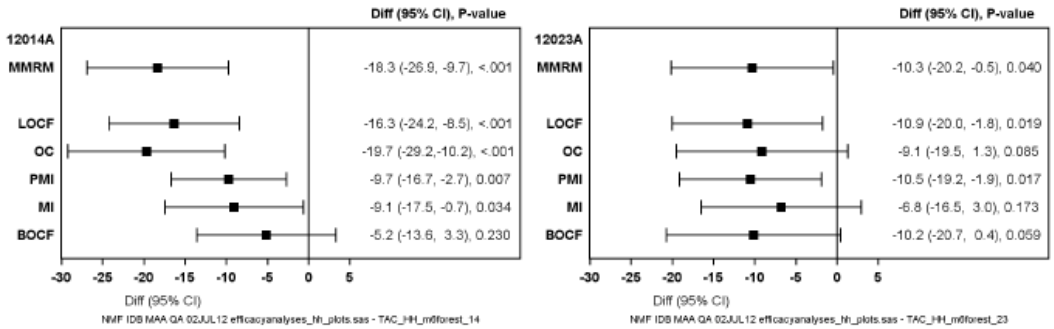


Left: ESENSE1; right: ESENSE2.

CI = confidence interval; BOCF = baseline observation carried forward; DRL = drinking risk level; FAS = full analysis set; HDD = heavy drinking day; LOCF = last observation carried forward; MI = multiple imputation; MMRM = mixed model repeated measures; OC = observed cases; PMI = placebo mean imputation.

Note: HDDs are shown as days per month.

Figure B16. Sensitivity analyses: changes from baseline to month 6 in TAC (FAS) in patients with a high/very high DRL at baseline and randomisation (ESENSE1 and ESENSE2)



Left: ESENSE1; right: ESENSE2.

CI = confidence interval; BOCF = baseline observation carried forward; DRL = drinking risk level; FAS = full analysis set; LOCF = last observation carried forward; MI = multiple imputation; MMRM = mixed model repeated measures; OC = observed cases; PMI = placebo mean imputation; TAC = total alcohol consumption.

Note: TAC is shown as grams per day.

The SAG to the EMA confirmed that the effect size of nalmefene was clinically meaningful. Additionally, the SAG recognised the validity of the post hoc analysis defining the licensed population. Whilst it was acknowledged that post hoc analyses are not ideal, it was stated that they are commonly used in

clinical trials for psychiatric drugs, given the high dropout rates encountered in these populations. The SAG also acknowledged that the reduction in alcohol consumption was an appropriate goal in a subgroup of alcohol-dependent patients with high/very high DRL without physiologic signs of withdrawal and not requiring any immediate detoxification procedure. To avoid misleading clinicians and to minimise off-label use, the group emphasised that the therapeutic indications should clearly instruct physicians (including GPs) to easily recognise the patients who could be the target of the drug (EMA, 2012).

The SAG also confirmed that the study population was representative of the population for whom nalmefene was proposed to be prescribed. Based on the data provided, patients with high/very high DRL were more likely to be the licensed population who could benefit from nalmefene treatment. Overall, there were no SAEs causing major safety concerns (EMA, 2012).

Limitations

In all three studies, individuals with severe medical conditions were excluded. In ESENSE1 and ESENSE2, psychiatric comorbidities were also an exclusion criterion (in the SENSE study, psychiatric comorbidities, such as depression, anxiety, social phobia, and insomnia, were allowed in the study). This limited the transferability of the results to the real-life setting where many alcohol-dependent patients have diagnosed medical conditions and/or psychiatric comorbidities.

For the total population, the differences in treatment effect between nalmefene and placebo and the reduction in alcohol consumption in terms of reduction in HDDs and TAC were inconsistent across the various sensitivity analyses (MMRM, last observation carried forward [LOCF], observed cases [OC], placebo mean imputation [PMI], multiple imputation [MI], and baseline observation carried forward [BOCF]), and there was a degree of uncertainty regarding the precise magnitude of the beneficial effects (or which analytical method was best suited to measure it) and their clinical relevance in the total population. Additionally, interpretation of the efficacy results observed was complicated, because a considerable number of subjects considerably reduced their alcohol consumption during the 1- to 2-week period between screening and randomisation. In these prerandomised reducers, there was virtually no space for further improvement either by BRENDA interventions or IMP intake.

Therefore, post hoc subgroup analyses were performed to substantiate the clinical efficacy and the clinical relevance of nalmefene, particularly in order to define a population in which the benefit of nalmefene would be greatest. A post hoc subgroup analysis was performed including patients with high/very high DRL at baseline who maintained a high/very high DRL at randomisation. A number of analytical methods were used to evaluate the data (MMRM, LOCF, OC, PMI, MI, and BOCF). The withdrawal rate in the trials rendered imputation of missing data an important issue when determining statistical significance of primary efficacy endpoints. Nevertheless, the proportion of patients who withdrew in the nalmefene clinical trial programme was comparable to that in other placebo-controlled clinical studies conducted in

patients with alcohol dependence over the last 10 years (e.g., Combine study, 2006; Anton et al., 2004; EMA, 2012).

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The predefined co-primary, key secondary, and other important secondary outcome measures, as well as the major inclusion/exclusion criteria and diagnosis tool (DSM-IV-TR) from the Lundbeck-sponsored phase 3 nalmefene trials, were in accordance with the recommendations in the EMA guideline on the development of medicinal products for the treatment of alcohol dependence (EMA, 2010).

On 30 May 2008, Lundbeck obtained EMA Scientific Advice on the clinical development programme for nalmefene and the design of the pivotal phase 3 clinical trials. On 18 February 2010, the CHMP adopted the EMA guideline on the development of medicinal products for the treatment of alcohol dependence, which came into effect on 1 September 2010. According to these guidelines, if a study drug addresses the goal of clinically significant reduced alcohol (intermediate harm reduction approach involving significant moderation without prior detoxification), efficacy should be expressed by change to baseline in TAC per month (presented as amount of pure alcohol in grams per day) and by reduction in number of HDDs (defined as ≥ 60 g/day of pure alcohol in men and ≥ 40 g/day in women). Both are considered primary variables because both are associated with specific risks such as acute cardiovascular outcomes or accidents (EMA, 2010). Both of these outcomes were co-primary endpoints in ESENSE1 and ESENSE2, which were primary efficacy studies. The effects of nalmefene on the number of HDDs and TAC were evaluated as a primary objective of the 1-year safety and tolerability study (SENSE), following protocol amendment.

As per the EMA recommendations for harm reduction studies, the nalmefene trials conducted by Lundbeck had adequate length of study duration, adequate selection and assessment of outcomes (both primary and secondary outcomes), and analysis of the right patient population (with high/very high DRL at baseline and randomisation) (EMA, 2010).

For safety outcomes, in all three studies, adverse events were carefully monitored and characterised in relation to the duration and dose of treatment. In addition, clinical observations were supplemented by clinical tests such as liver tests, lipid parameters, blood pressure, and cardiac rhythm.

Direct evidence of the clinical relevance of a reduction in alcohol consumption as seen with nalmefene versus placebo is available from standardised effect sizes for the co-primary endpoints, responder analyses, improvement in CGI-I/CGI-S scores, improvement in liver enzymes, and improvement in physical and social functioning. Indirect evidence illustrates further how reduction in alcohol consumption is translated into harm reduction.

6.10.3.1 Direct evidence

Effect size

The standardised effect sizes (Cohen's d; based on MMRM analyses) between nalmefene and placebo in patients with a high/very high DRL at baseline and randomisation reported in ESENSE1 (HDD, 0.37; TAC, 0.46) and ESENSE2 (HDD, 0.27; TAC, 0.25) (van den Brink et al., 2013) were at least of the same order of magnitude as those reported for drinking variables for medicinal products approved in the European Union for a different indication (maintenance of abstinence) and within the range reported for approved medicinal products in other central nervous system indications (NICE, 2011; Leucht et al., 2012).

Responder analyses and number needed to treat to benefit

A reduction in alcohol consumption can be translated into an expected significant improved health outcome for the patient, using different responder definitions (EMA, 2010). As noted in Section 6.5, the responder analyses assessed from the three phase 3 nalmefene trials were in accordance with the analyses proposed by the EMA. In patients with a high/very high DRL at baseline and randomisation, the OR for response (MMRM analysis) was consistently statistically significantly in favour of nalmefene for the RLDRL analysis, the RSDRL analysis, and the R70 analysis in the pooled data from ESENSE1 and ESENSE2. For RSDRL, the proportion of responders was 57% in the nalmefene group and 42% in the placebo group, which translated to a number needed to treat to benefit (NNTB) of 7 patients. For RLDRL, the proportion of responders was 43% in the nalmefene group and 32% in the placebo group, which translated to an NNTB of 9 patients. Finally, in the R70 analysis, the proportion of responders was 38% for nalmefene and 26% for the placebo group, which translated to an NNTB of 9 patients.

Please refer to Section 6.5 for details of the responder analyses in the licensed population.

Improvement in CGI-I/CGI-S scores

The CGI-I and CGI-S scales allow the clinician to make a global evaluation of the patient's disease severity and overall functioning (Guy, 1976). This measure allows clinicians to examine the management of alcohol dependence with therapy over time and make necessary adjustments to the type of therapy. The CGI scales are routinely used to evaluate patients with alcohol dependence (Johnson et al., 2004; Yoon et al., 2006; Tolliver et al., 2012). The reduction in alcohol consumption in the patients with a high/very high DRL at baseline and randomisation following treatment with nalmefene translated to improvements in CGI-S and CGI-I scores from week 2 that were maintained throughout the treatment period, which reflected the global clinical judgement of the outcome by an expert clinician (see Section 6.5.3).

Improvement in liver enzymes markers status

Liver tests reflect enzyme induction as well as possible liver damage, helping to validate the improvements in self-reported alcohol consumption from the TLFB method. Liver tests are routinely used in clinical practice; however, no single laboratory marker definitely establishes chronic alcohol consumption (European Association for the Study of the Liver, 2012). Currently used biomarkers reflect only damage and can be confounded by age and other factors; thus, a combination of biomarkers is necessary (EMA, 2010). Both GGT and ALAT were monitored during the three pivotal nalmefene trials. The reduction in alcohol consumption in the patients with a high/very high DRL at baseline and randomisation following treatment with nalmefene translated into a greater decrease in liver enzymes (GGT and ALAT) relative to placebo (see Section 6.5.3).

Improvement in physical and social functioning

The SF-36 is a self-administered questionnaire used to monitor the impact of disease on the qualify of life. The SF-36 scales are widely used to evaluate quality of life in patients with alcohol dependence (Morgan et al., 2004; Lahmek et al., 2009).

Improvements were observed in HRQL with nalmefene compared with placebo, as measured by SF-36 and EQ-5D in the pooled ESENSE1 and ESENSE2 studies (Francois et al., 2013).

In the pooled ESENSE1 and ESENSE2 data, the SF-36 mental component score improvement at month 6 was significantly correlated to reduction in the number of HDDs and TAC ($P < 0.0001$) and was significantly larger for the nalmefene group compared with placebo ($P = 0.0008$): the mean (SD) changes from baseline were 5.74 (0.79) and 2.65 (0.78) in the nalmefene and placebo groups, respectively. The improvement at month 6 was also significantly larger for the nalmefene group compared with the placebo group for the physical component score (incremental of 1.23 ± 0.55; $P = 0.0259$). Furthermore, the mean change from baseline for nalmefene compared with placebo was 3.46 points ($P = 0.0124$) for the health state score and 0.03 points ($P = 0.0445$) for the utility index score.

These outcomes in terms of improvement from treatment in HRQOL are likely to be underestimated. It is important to determine how well the changes in an alcohol-dependent patient's quality of life can be captured. In particular, how well can the patient's improvement in terms of level and frequency of drinking become linked with changes in quality of life measures in the context of RCTs. A systematic review of quality of life instruments used as outcome measures in RCTs for alcohol-dependence treatment by Luquiens and colleagues (2012) reported that available instruments measuring quality of life lack sensitivity to outcome changes in alcohol dependence. Eight instruments were identified in this review:

- SF-36
- 12-item Short-form Health Survey [SF-12]

- WHO Quality of Life 26-item questionnaire [WHO-QOL-26]
- EQ-5D
- Alcohol Problems Questionnaire [APQ]
- KoskenvuoQoL Scale
- Visual Analogue Scale Quality of Life [VASQoL]
- TOMHS-HWBS

The most frequently used instrument to measure HRQL in the included studies was the SF-36.

The HRQL instruments identified in this systematic review investigated domains such as relationships with others, activities, physical state, psychological state, financial concerns, medical care, legal problems, and satisfaction with life; however, no one instrument identified in the systematic review covered all of these domains. In conclusion, this study highlighted the heterogeneity of the instruments to measure quality of life used in alcohol-dependent patients and revealed that the information collected may not be relevant or accurate for this specific patient population.

6.10.3.2 Indirect evidence

Harm reduction based on predictive microsimulation model

As part of the EMA regulatory submission package, a microsimulation model was conducted by Lundbeck and external contributors to evaluate the consequences of HDDs and TAC in terms of the incidence of alcohol-attributable diseases and injuries. Alcohol consumption was simulated, day by day, at patient level for 12 months, using statistical equations estimated from nalmefene clinical trial data. The statistical methods used for the simulation were found by the SAG to the EMA to be acceptable. Individual patient data for HDDs and TAC were simulated. Model selection for odds of drinking and count data for alcohol consumption was based more on empirical considerations than on theoretical assumptions and was considered acceptable. The model was used to generate a dataset of 200,000 untreated alcohol-dependent patients.

The model was used to generate a data set of 200,000 untreated alcohol-dependent patients. Using this data set, it was possible to translate alcohol reduction into harm reduction by modelling the consequences of alcohol reduction in terms of health and social events, thus comparing probabilities of events between different groups of patients (according to the number of HDDs and TAC over 12 months). The implementation in the microsimulation model of alcohol-attributable health and social events was performed using a method developed independently by the Social and Epidemiological Research Department of the Centre for Addiction and Mental Health in Toronto, Canada.

The detail of the method is available on request.

The number of HDDs over 1 year was divided into eight categories with a range of 20 HDDs over a year in order to represent a difference of 2 monthly

HDDs versus placebo. For all diseases or injuries, the number of events increased with the number of HDDs per year both for males and females. The TAC per year was divided into 14 categories with a range of 3,000 g over a year in order to represent the difference of a monthly average of 10 g/day versus placebo. Table B42 and Table B43 present the distribution of events.

Table B42. Number of events per 100,000 patient-years by category of number of HDDs (males and females)

HDD range (days)	Ischaemic heart disease	Ischaemic stroke	Traffic injuries	Other injuries	Cirrhosis	Pancreatitis	Pneumonia	Haemorrhagic stroke
< 100	1,563	494	303	2,434	330	141	1,827	149
100-120	1,707	538	398	3,085	428	188	1,957	171
120-140	1,819	572	465	3,602	505	235	2,046	188
140-160	1,928	606	531	4,112	582	291	2,120	203
160-180	2,027	637	598	4,553	686	391	2,217	223
180-200	2,118	666	668	4,953	836	596	2,340	248
200-220	2,211	695	747	5,361	1,084	1,136	2,523	284
> 220	2,300	724	822	5,742	1,378	2,251	2,705	323

HDD = heavy drinking day.

Source: EMA, 2012.

Table B43. Number of events per 100,000 patient-years by TAC category (males and females)

TAC range (g)	Ischaemic heart disease	Ischaemic stroke	Traffic injuries	Other injuries	Cirrhosis	Pancreatitis	Pneumonia	Haemorrhagic stroke
< 15,000	1,465	467	239	2,034	269	116	1,731	134
15,000-18,000	1,562	498	304	2,492	322	132	1,812	149
18,000-21,000	1,640	524	358	2,881	370	150	1,879	161
21,000-24,000	1,721	551	412	3,278	424	175	1,950	174
24,000-27,000	1,810	579	467	3,691	483	206	2,022	189
27,000-30,000	1,895	605	519	4,071	548	248	2,095	204
30,000-33,000	1,964	626	568	4,383	621	303	2,173	221
33,000-36,000	2,024	645	613	4,652	703	380	2,254	239
36,000-39,000	2,076	661	655	4,887	794	485	2,340	259
39,000-42,000	2,122	675	693	5,089	899	636	2,435	280
42,000-45,000	2,157	686	726	5,248	1,017	866	2,528	303
≥ 45,000	2,216	704	773	5,508	1,234	1,435	2,691	336

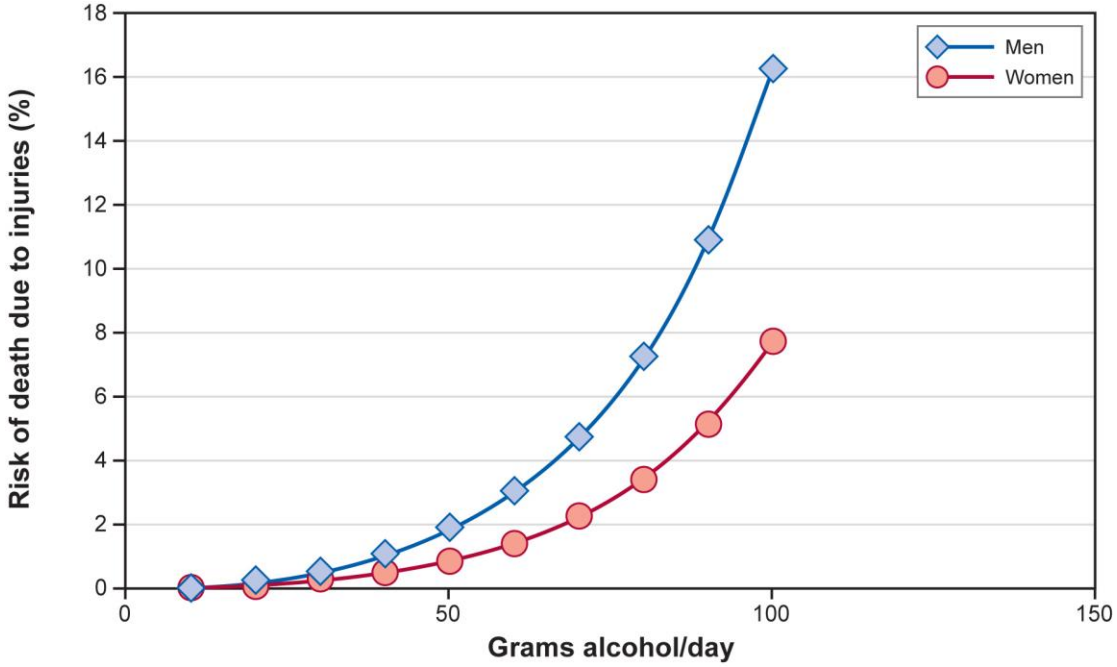
TAC = total alcohol consumption.

Source: EMA, 2012.

The results of the model are presented in the EPAR (Figure B17) where the SAG to the EMA concluded that alcohol consumption has an exponential relationship to harmful events, stating the following:

> "The modelling data represent the net treatment effect of nalmefene over placebo and point to a clinically relevant reduction of alcohol-associated events like transport injuries, ischemic heart disease, pancreatitis, etc. if alcohol consumption is reduced to the degree that was achieved with nalmefene in the chosen patient collective. The model showed that even a moderate decrease in drinking levels might be associated with a decrease in both harmful events and a decrease in relative risk of the medical issues typically linked to excessive alcohol drinking." (EMA, 2012)

Figure B17. Relationship between alcohol consumption and risk of death due to injuries



6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

As described in Section 6.10.2, all three nalmefene pivotal studies were conducted in different regions within Europe and therefore accounted for differences across countries in disease management and drinking patterns.

In the three nalmefene phase 3 studies (ESENSE1, ESENSE2, and SENSE), nalmefene was administered at the same dose and frequency as the licensed dose that will be used in clinical practice (18 mg nalmefene as-needed).

The licensed population for nalmefene is adult patients with alcohol dependence who have a high DRL, without physical withdrawal symptoms, who do not require immediate detoxification, and who continue to have a high DRL 2 weeks after initial assessment. This patient population corresponds with patients from the nalmefene clinical trial programme who had a high/very high DRL at baseline (screening) and randomisation. The SAG confirmed that this patient population from the clinical trials is representative of the population for whom nalmefene is proposed to be prescribed (EMA, 2012).

The nalmefene product label states that nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. In the nalmefene clinical trial programme, this psychosocial support was delivered in the form of BRENDA. BRENDA, a motivational and adherence-enhancing intervention, emphasises the importance of adherence to treatment by providing positive feedback and help in solving difficulties with adherence. BRENDA was administered to all the patients throughout the treatment period in all three studies, in accordance with the EMA guideline on the development of medicinal products for the treatment of alcohol dependence, which states that standardised psychosocial interventions should be allowed in alcohol-dependence studies and kept to a constant and low level for all patients (EMA, 2010). None of the BRENDA components are specific to any one illness (Starosta et al., 2006), and the components constitute what is likely already performed by GPs and specialists when treating patients for alcohol dependence. BRENDA is one of several forms of psychosocial support that can be given with nalmefene; in routine clinical practice, BRENDA can be replaced by any psychosocial intervention focused on treatment adherence and reducing alcohol consumption.

BRENDA is comparable with psychosocial support and is very similar to what occurs in clinical practice in managing chronic diseases (such as diabetes, hypertension, and inflammatory bowel disease) where healthcare providers address a wide variety of behavioural problems with a combination of clinical advice (i.e., biofeedback together with expressing caring, encouraging progress, positive reinforcement, and educating the patient on the disease) and medication management.

The current NICE guideline recommends psychosocial intervention (including cognitive behavioural therapies, behavioural therapies, social network and environment-based therapies, or behavioural couples therapy) for the treatment of alcohol-dependent patients with a treatment goal of alcohol reduction (NICE, 2011a). While these can be intensive, some kind of brief intervention is the most commonly applied form of psychosocial intervention used in clinical practice in England and Wales. This may be delivered in a primary care/tier 2 or tier 3 setting and usually consists of assessment followed by the provision of information and advice (Expert opinion, Lundbeck Data on File, 2014). Therefore, continuous psychosocial support, such as that

described in the nalmefene licence and delivered during the phase 3 studies, would be comparable to delivering an extended brief intervention during regular and ongoing patient assessment visits.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

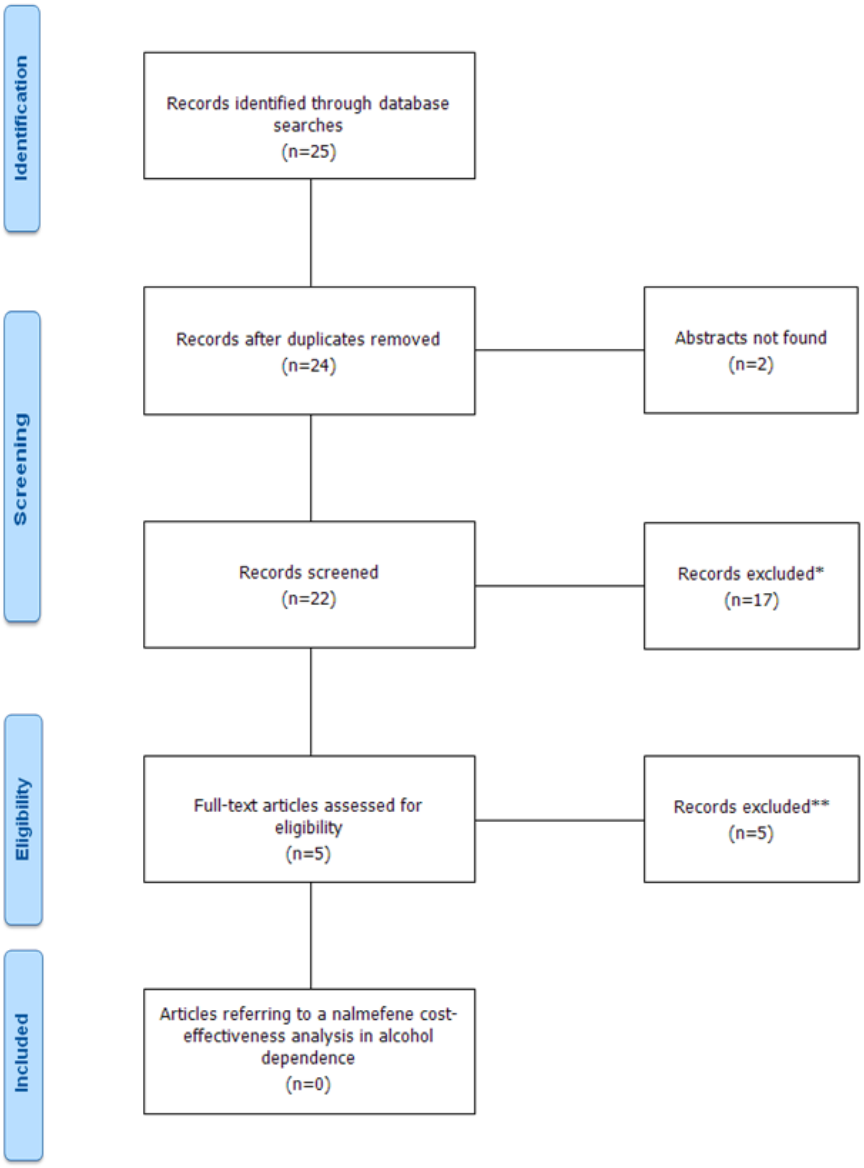
7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in Section 10.10, Appendix 10.

A search of the published medical literature was performed in January 2013 to identify published cost-effectiveness analyses for nalmefene in alcohol dependence in the following databases: EMBASE, Medline and Medline-in-process, and the Cochrane Collaboration.

The literature search yielded 25 citations. After the removal of three citations (one duplicate and two citations where no abstract could be obtained), 22 records remained. The abstracts of these 22 records were screened for any mention of an alcohol use disorder AND pharmacological intervention AND cost. Based on these criteria, 17 further records were excluded and 5 records were selected for full-text review.

After reviewing the full text of these 5 articles, it could be concluded that no nalmefene cost-effectiveness analyses in alcohol dependence had been published. Details of abstracts reviewed and studies excluded at each stage of this review are presented in the PRISMA flow diagram in Figure B18.

Figure B18. PRISMA diagram for systematic review of cost-effectiveness studies



* Record excluded if no mention of an alcohol use disorder AND pharmacological intervention AND cost in the abstract.

** Record excluded if no reference to a nalmefene cost-effectiveness analysis in alcohol dependence.

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

As the review concluded that no nalmefene cost-effectiveness analyses in alcohol dependence had been published, no studies have been described in this section.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996) or Philips et al. (2004). For a suggested format based on Drummond and Jefferson (1996), please see Section 10.11, Appendix 11.

As the review concluded that no nalmefene cost-effectiveness analyses in alcohol dependence had been published, no quality assessment has been performed.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in Sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The de novo economic evaluation was designed to assess the cost-effectiveness of nalmefene in the treatment of alcohol dependence.

The population in the model consists of a patient cohort with alcohol dependence and defined drinking levels according to WHO's definition of drinking-risk levels (Table B44) (WHO, 2000). The model was developed based on the clinical trials of nalmefene: the nalmefene + BRENDA arm from the trials being used for modelling the nalmefene + PI cohort and the placebo + BRENDA arm from the trials being used for modelling the psychosocial intervention cohort Table B45.

Table B44. Categorical levels for average volume of pure alcohol per day for women and men

DRL[a]	Total Consumption (g/day)	
	Men	Women
Very high risk	> 100	> 60
High risk	> 60-100	> 40-60
Medium risk	> 40-60	> 20-40
Low risk	1-40	1-20
Abstinent	0	0

DRL = drinking risk level.

[a] The risk applies to alcohol consumption on a single day in relation to acute problems and to chronic harm.

Source: (World Health Organization, 2000).

Table B45. Patient population in ESENSE1, ESENSE2, and SENSE trials (high and very high WHO DRL at screening and randomisation)

Characteristic	Pooled Estimates
Age (mean years)	48
Sex (% men)	69
DRL (%)	
Very high risk	58
High risk	42

DRL = drinking risk level; WHO = World Health Organization.

The current analysis was based on pooled estimates of patients from ESENSE1 (6-month study), ESENSE2 (6-month study), and SENSE (1-year study) that included patients with high/very high DRL at screening and randomisation (licensed population) (Section 1.3). The key efficacy endpoints in all three studies were the reduction in number of HDDs per month and daily TAC. The 1-year SENSE study was not primarily designed to demonstrate the efficacy of nalmefene, and so for this model it was pooled with ESENSE1 and ESENSE2 for 6 months, allowing the use of all efficacy evidence available to assess nalmefene in the context of its licensed indication and allowing the use of efficacy data of the use of nalmefene up to 1 year. The pooled primary efficacy endpoints of the three studies as used in the context of this cost-effectiveness analysis are presented in Table B46, showing the statistical significance of the difference between compared treatment arms for both primary endpoints. Additionally, the responder analysis pooling the three studies (RSDRL: response defined as a downward shift from baseline in DRL by two risk categories) is presented in Table B47, showing again statistical significance of the difference between compared treatment arms.

Table B46. Main treatment period: adjusted change from baseline I to month 6 in monthly HDDs & TAC (FAS, OC, MMRM) – Study 12014A, 12023A & 12013A - high/very high DRL at baseline & randomisation

	Number of participants at baseline		Endpoint	Mean difference to placebo in the change from baseline	95% CI	*P* value
	Nalmefene	Placebo				
Pooled studies (Month 6) (ESENSE1 & 2, SENSE)	460	364	HDD	−3.01 days/month	−4.36; −1.66	< 0.0001
			TAC	−14.22 g/day	−19.96; −8.47	< 0.0001
SENSE (Month 13)	141	42	HDD	−3.60 HDDs/month	−6.52; −0.67	0.0164
			TAC	−17.31 g/day	−30.87; −3.76	0.0129

CI = confidence interval; DRL = drinking risk level; FAS = full analysis set; HDD = heavy drinking day; MMRM = mixed model repeated measures; OC = observed cases; TAC = total alcohol consumption.

Table B47. Responder analysis of a downward shift in RSDRL at month 6 (LREG, FAS, OC) – pooled population ESENSE1, ESENSE2 and SENSE

RSDRL at Month 6 (LREG, FAS, OC	Number of participants at baseline		Endpoint	Odds ratio for response at month 6	95% CI	*P* value
	Nalmefene + PI	Placebo + PI				
Pooled studies Month 6 (ESENSE1, ESENSE2 and SENSE)	460	364	RSDRL	1.55	1.06; 2.25	0.0022

CI = confidence interval; FAS = full analysis set; OC = observed cases; PI = psychosocial intervention; RSDRL = response defined as a two category downward shift from baseline in drinking risk level.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

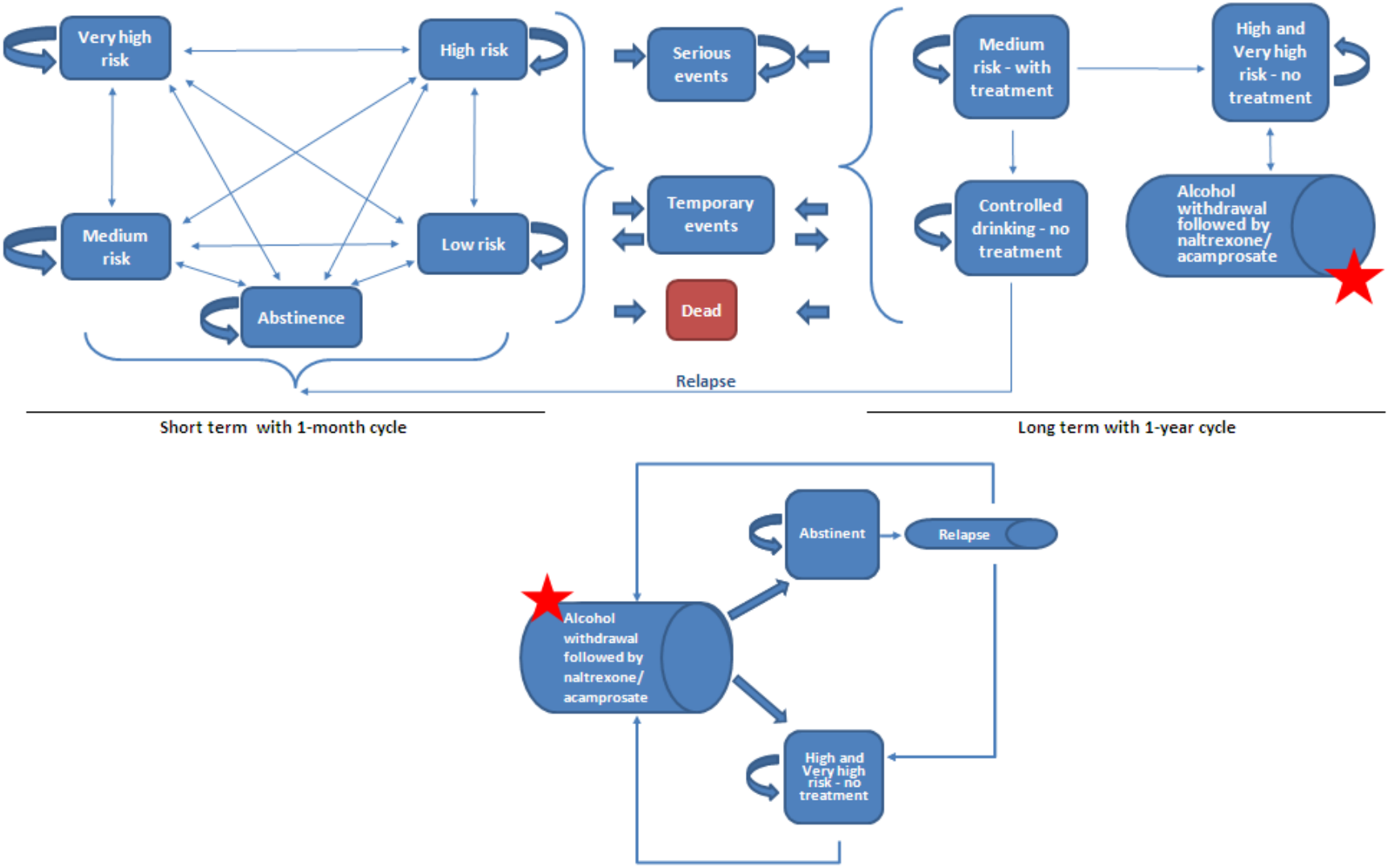
The structure of the cost-effectiveness decision model (Figure B19) is based on a Markov approach and consists of a short-term phase (1-year, based on clinical trials assessing nalmefene) and a long-term phase (beyond the initial 1-year within-trial time horizon and up to 5 years, which extrapolates the results of the trials. The cycle length is 1 month in the short-term phase and 1 year in the long-term phase.

The short-term 1-year phase accounts for treatment efficacy and the patient's adherence whether the treatment is discontinued as observed in clinical trials, and it accounts for the incidence of alcohol-attributable harmful events and deaths. A 1-month (28-day) cycle length was applied to be aligned with the phase 3 nalmefene clinical studies, with patient follow-up (TAC over 28 days; number of HDDs over 28 days), and with common clinical management.

The long-term phase models the maintenance of effect of treatment, patient progression, and the incidence of alcohol-attributable harmful events and deaths. For the long-term phase, a 1-year cycle length was applied. The availability of reliable clinical data allowed for the application of a 1-year cycle length, particularly with regard to (1) the available evidence for the maintenance of effect and probability of recurrence of heavy drinking after initial response to the treatment by patients and (2) the available evidence of efficacy for the second-line treatment option to which patients are directed if their initial treatment with nalmefene + PI or PI (assisted withdrawal followed by naltrexone or acamprosate + PI) has failed. A 1-year cycle length also reduces the number of assumptions needed, allowing a limited number of simple assumptions after the trial period. Additionally, the simple approach taken is believed to limit as far as possible the uncertainty related to the extrapolation of the outcomes from the phase 3 studies.

The model structure was the same for compared treatment strategies (nalmefene + PI vs. PI). The transition probabilities between drinking-dependent health states, and thus the risk of alcohol-attributable harmful events, are dependent upon the treatment alternative.

Figure B19. Summary of the health states incorporated in the model



7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in Section 2.5.

The model has been structured to reflect the treatment pathway for the treatment of alcohol dependence in England and Wales. As outlined in Section 2.5 and aligned with the NICE CG115 (NICE, 2011a), patients with alcohol dependence who do not require immediate detoxification may be suitable for a management strategy of reduction of alcohol consumption. Psychosocial intervention is the mainstay of treatment for alcohol dependence irrespective of care setting and has been shown to be effective in reducing alcohol consumption (NICE, 2011a). Thus, in line with current treatment pathways and proposed positioning for nalmefene within clinical practice (Figure A4 and Figure A5), the model has been structured to compare treatments of patients with mild alcohol dependence who continue to have a high DRL and no physical withdrawal symptoms following a 2-week assessment period. In this first-line treatment, the model compares the current mainstay of treatment, psychosocial intervention, with nalmefene + PI. Additionally, in line with the proposed treatment pathway and Figure A5, patients who fail to control their drinking levels after treatment with nalmefene + PI or with PI are believed to transition to a treatment goal of abstinence and be offered acamprosate or oral naltrexone + PI for relapse prevention following successful alcohol withdrawal/detoxification.

7.2.4 Please define what the health states in the model are meant to capture.

Figure B19 illustrates the model structure and the different health states patients can go through for the entire 5-year time horizon. Health states can be subdivided in three categories: short-term health states (drinking health states), long-term health states (including drinking health states and the second-line treatment option), and alcohol-attributable harms health states (including alcohol-attributable diseases, injuries, and death).

Short-term health states (first year)

As shown in Figure B19, the model for the first year of treatment effect considers five key drinking level health states, which represent the categories proposed by the WHO (2000) to define the levels of alcohol consumption by risk of alcohol-attributable acute and chronic harms and abstinence. These levels are used in clinical trials and in clinical practice for patients' assessment and management (Table B44).

The patient cohort begins in the model at a designated drinking risk level, which is either high or very high in line with the indication for use of nalmefene. The proportion is the same as the pooled proportion at randomisation for ESENSE1, ESENSE2, and SENSE (described in Section 7.2.1). From this initial drinking level, after each 1-month (28-day) cycle each patient can move among the five drinking levels at treatment-specific rates for the first year of the model for 13 cycles. Additionally, after every cycle, patients can move to an alcohol-attributable harmful-event health state (including death) in the model. Monthly transitions among drinking levels and

alcohol-attributable harmful-event health states continue monthly for the first year.

Long-term health states (2-5 years)

After the first year, three yearly health states relating to drinking levels are considered, informed by the evidence used for maintenance of effect and probability of recurrence to heavy drinking (Taylor et al., 1985), which aligns with clinical practice: controlled drinking, medium-risk drinking, and high/very high-risk drinking. The third health state, high/very high-risk drinking, leads to the second-line treatment option (alcohol withdrawal followed by naltrexone or acamprosate + PI).

Controlled-drinking

The patient cohort that is in the low-risk drinking level or is abstinent after 12 months (and has not discontinued treatment) is assumed to be in control of their drinking and thus these patients discontinue all treatment.

To account for the possibility that patients with controlled-drinking may resume to heavy drinking (go back to high/very high drinking levels), a yearly proportion of patients are modelled to relapse and receive a second round of treatment (these patients go back to the short-term 1-year model). Patients who relapse return to the same treatment in which they were initially successful controlling their alcohol intake (i.e., nalmefene + PI or PI). The proportions of patients who relapse are distributed among the same drinking levels as are the initial patient cohort in the model (high or very high WHO DRL). When a patient relapses and goes back to treatment, the same monthly probability transitions as when the patient initiated treatment for the first time are conservatively applied, without considering the potential higher likelihood for this patient to respond to treatment due to previous response. The patients not experiencing a relapse continue in the controlled-drinking state for the remainder of the model.

Medium-risk drinking

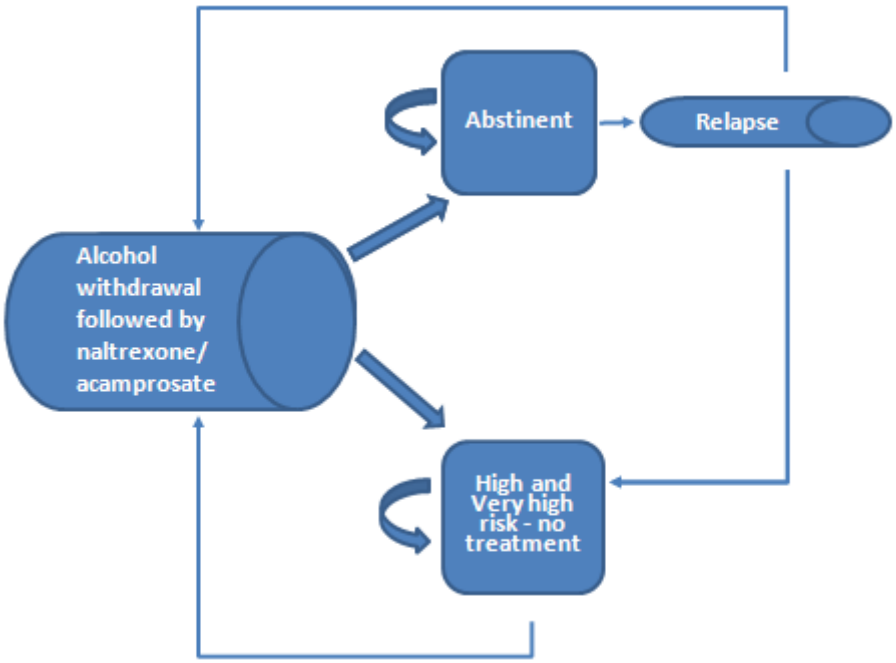
The patient cohort in the medium-risk drinking level after 12 months is assumed to respond to treatment, but not sufficiently so as to stop treatment altogether; these patients therefore remain on treatment. According to clinical experts in England and Wales consulted by Lundbeck, this is aligned with clinical practice considering the risk of acute and chronic harms for this level of drinking. It was also judged that only a small proportion of patients would be allowed, in real-life clinical practice, to continue treatment after a period of 1 year to derive additional benefit from treatment with nalmefene + PI. This is consistent with the SENSE study, which showed that 12% of patients in the nalmefene + PI arm and 14% of patients in the PI arm were at medium-risk drinking levels at 1 year (this proportion excludes patients having discontinued treatment during the year). Patients in the medium-risk drinking level with continuous nalmefene + PI treatment can transition to controlled drinking or high and very high drinking.

High/very high-risk drinking and second-line treatment option

The patient cohort that is in the high- or very high-risk drinking level after 12 months (viewed as non-responders) is modelled to discontinue current treatment and change treatment strategy to an abstinence-orientated approach, which includes assisted alcohol withdrawal followed by acamprosate or oral naltrexone + PI for relapse prevention. This is aligned with the NICE CG115 (NICE, 2011a) recommendations, considering that these patients' alcohol dependence is likely to have evolved in severity during their unsuccessful year of treatment.

In the model, this whole secondary treatment sequence is accessed via a tunnel state based on the combined effect of alcohol withdrawal and acamprosate or oral naltrexone + PI (Figure B20).

Figure B20. Secondary treatment sequence: alcohol withdrawal followed by acamprosate or oral naltrexone + PI



Alcohol-attributable harms health states

In the model, the patient cohort is assumed to have an underlying risk for harmful events due to alcohol consumption. Harmful events due to alcohol include acute and chronic events or diseases and can lead to morbidity, mortality, and costs. Each patient's risk of experiencing these events is dependent on the patient's WHO DRL. 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. The implementation of these events was carried out in the same manner as for the microsimulation model presented to the EMA, (which is discussed in Section 6.10.3.2) above. This method was developed independently by the Social and Epidemiological Research (SER) Department at the Centre for Addiction and Mental Health in Toronto, Canada.

Alcohol-attributable harmful events included in the model were divided in two categories based on their physiopathology of occurrence with regard to level and pattern of alcohol consumption:

- Immediate-drinking events: alcohol-attributable diseases or injuries incurred from a single episode of heavy alcohol consumption. These events included transport injuries, other injuries, ischemic stroke, and ischemic heart disease.
- Continuous-drinking events: alcohol-attributable diseases associated with continuous alcohol consumption over time. These events included liver cirrhosis, pancreatitis, lower respiratory infections, and haemorrhagic stroke (Table B48).

Table B48. Alcohol-attributable harmful events

Type	Event
Continuous-drinking events	Lower respiratory infections
	Haemorrhagic stroke
	Cirrhosis of the liver
	Pancreatitis
Immediate-drinking events	Ischaemic heart disease
	Ischaemic stroke
	Transport injuries
	Injuries other than from transport

Because of the impact the modelled alcohol-attributable diseases and injuries have on the patient situation, these were modelled in two ways and thus separated into serious events and temporary events (Figure B19).

Serious events

Once a patient cohort experiences one of the serious events outlined in Table B49, that cohort is removed from the portion of the model that uses health states defined by drinking levels. This proportion of patients continues in a postevent state for the rest of the model's timeframe. The model then estimates the cohort's quality-adjusted life-years (QALYs) and costs on the basis of serious events. This is considering that the seriousness of these diseases precludes the treatment of alcohol dependence. Also, the cost and QALY decrement for these harmful events are more important than for the drinking-related event. Additionally, by modelling these events in postevent states, the patients can have only one serious event. Thus, we avoid having

to account in the model for a secondary conditional probability (e.g., the conditional probability of a patient having ischaemic heart disease after the initial event of a stroke). This is a conservative assumption with regard to the treatment effect of nalmefene.

Temporary events

The temporary events are modelled through a tunnel state. In a tunnel state, the proportion of patients pass through the state (or event) while acquiring costs and an immediate decrement in QALYs, in addition to other costs (alcohol treatment costs) and QALYs incurred by the drinking level health states. However, the state or event will not produce any long-term effects as long as the patient survives the tunnel state. This tunnel state lasts 1 month, an assumption based on the cycle length for the short-term phase of the model.

Death

Additionally, in the model and over the course of the model time horizon, patients can move from any health state to the death state; patients can die from either alcohol-attributable harmful events or all-cause mortality. Death from alcohol-attributable harmful events was modelled in the same way as the diseases/injuries itself as explained above.

Table B49. Alcohol-attributable harmful events

Type	Event	Modelled as
Serious events	Ischaemic heart disease	Post-event state
	Haemorrhagic stroke	Post-event state
	Ischaemic stroke	Post-event state
	Cirrhosis of the liver	Post-event state
	Pancreatitis	Post-event state
Temporary events	Lower respiratory infections	Tunnel state
	Transport injuries	Tunnel state
	Injuries other than from transport	Tunnel state

Modelling drop-outs from the nalmefene clinical trials

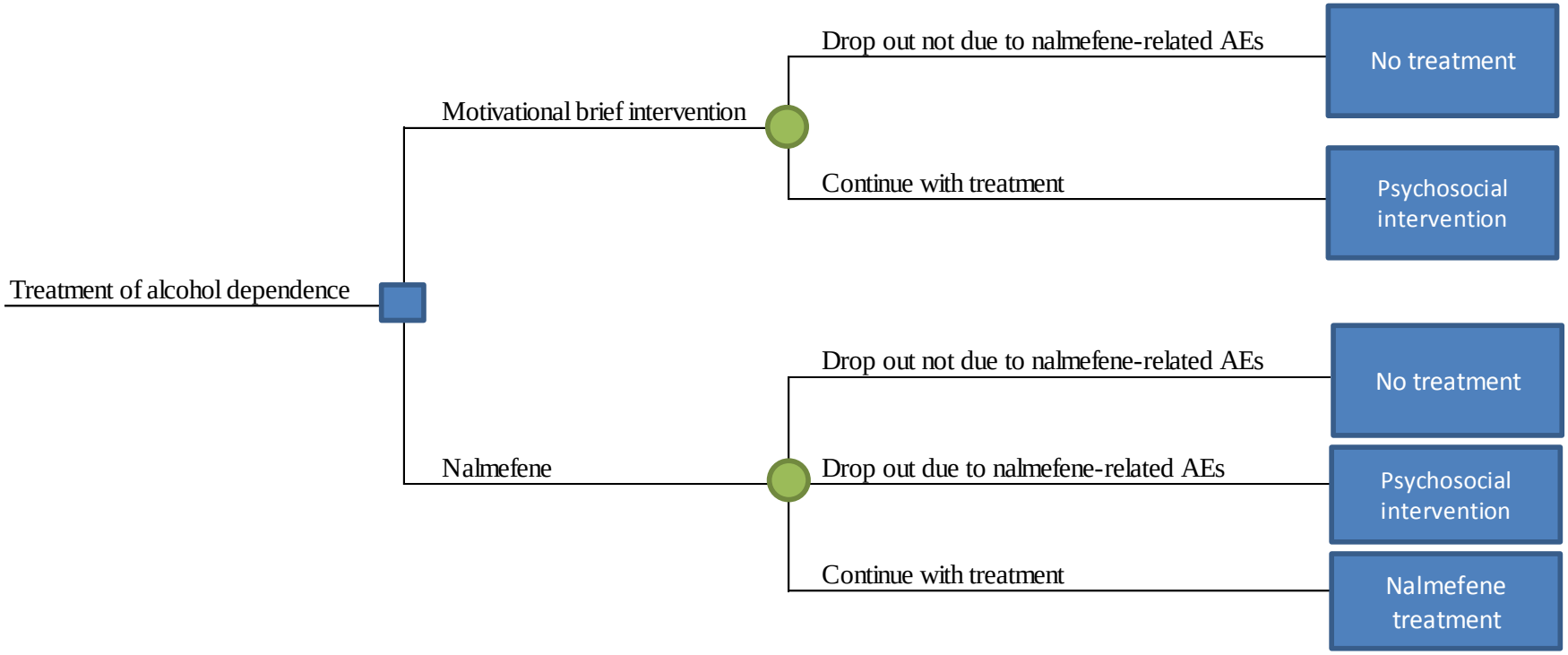
In addition to the core model structure and the risk of alcohol-attributable harmful events, the model also incorporates risks of dropping out due to adverse events from nalmefene or due to other reasons. This is based on data from the three pooled nalmefene clinical trials. In the model, an adverse event can cause the patient cohort to change treatment or to quit treatment, depending on the treatment and the source of adverse event (Figure B21).

For the nalmefene + PI treatment strategy, patients who drop out due to nalmefene-related adverse events (such as nausea, dizziness, insomnia, and headache) stay in the nalmefene treatment arm, but they have their treatment changed to receive a PI (the effect of PI is applied to these patients, these patients being still accounted for in the nalmefene + PI cohort). This approach

assumes that the patient is willing to continue treatment for their alcohol dependence, but is unable to continue nalmefene treatment due to side effects. Patients who change treatment due to nalmefene-related adverse events transition to their corresponding drinking level for the PI treatment strategy and continue to be modelled in the same way, with corresponding transition probabilities from the time of dropout (being still accounted in the nalmefene + PI cohort). In continuing with PI, it is still possible for the patient to drop out for other reasons, such as alcohol-related harmful events or death.

For both the nalmefene + PI treatment strategy and the PI strategy, patients who drop out due to other reasons (i.e., reasons other than nalmefene-related adverse events, such as withdrawal of consent, protocol violation and lost to follow-up, noncompliance, and lack of efficacy) have their treatment changed to ‘no treatment’ (Figure B21). Patients who change to no treatment due to other than nalmefene-related adverse events transition immediately to high or very high WHO DRL with the same distribution as at entry into the model. This is a conservative assumption, which does not account for the potential maintenance of effect of the treatment after a drop-out occurs. These patients then remain in this state for the rest of the model’s time frame.

Figure B21. Drop-out sequence



AE = adverse event.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in Section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to Section 2.1.

As outlined in Section 2.1, alcohol dependence accounted for more than 70% of the overall alcohol-attributable net mortality before the age of 65 years in the European Union (Rehm and Shield, 2012). 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 (Rehm and Shield, 2012). However, reduction of drinking, especially of heavy drinking, is associated with a reduction in alcohol-attributable harms, with the reduction being highest for the heaviest drinking category (Rehm and Roerecke, 2013). Thus, treatment of alcohol dependence that reduces levels of consumption either to abstinence or by a sizable reduction of heavy drinking (Rehm and Gual, 2013) can also have a significant effect on the harms related to alcohol dependence. The model has been structured specifically to capture the treatment effect of nalmefene + PI and PI with regard to reduction of drinking with health states defined by DRL (see Sections 7.2.2 and 7.2.3, and Figure B19). In addition it specifically models how the transition between DRL-dependent health states affects the relative risk for mortality, morbidity, and social consequences such as crime.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B50. Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Short-term time horizon (within-trial, 1-year)	The short-term 1-year phase accounts for the patient's drinking pattern while in treatment; patient's adherence, whether the treatment is discontinued as observed in clinical trials; and the incidence of alcohol-attributable harmful events and deaths. The short-term 1-year phase specifically follows the duration of the clinical trials and the effectiveness demonstrated in them.	ESENSE1 (Lundbeck, 2012b) ESENSE2 (Lundbeck, 2012c) SENSE (Lundbeck, 2012a)
	Long-term time horizon (5 years)	The long-term phase (after the first year) models three yearly health states relating to drinking levels are considered informed by the evidence used for maintenance of effect and probability of recurrence to heavy drinking what aligns with clinical practice: controlled drinking, medium-risk drinking, and high/very high-risk drinking. The third health state, high/very high-risk drinking, leads to the second-line treatment option (alcohol withdrawal followed by naltrexone or acamprosate + PI).	Barbosa et al., 2010 Taylor et al., 1985
	Overall time horizon	The base-case analysis in the model used a 5-year time horizon. This time horizon is judged sufficiently long to reflect appropriately the differences in costs or outcomes between the technologies being compared. This time horizon was believed to capture the benefit of compared interventions without reaching unacceptable uncertainty in terms of patients' long-term drinking behaviour, treatment needs, and development of chronic diseases from long-term alcohol consumption. This uncertainty would in turn lead to an increased uncertainty in terms of cumulative costs and QALYs incurred for the compared treatment groups. Additionally, limiting this extrapolation to 5 years avoided favouring nalmefene unfairly over psychosocial intervention, particularly as the extrapolation of outcomes was directly associated with the proportion of patients in the different drinking levels at 12 months (end of the within-trial time horizon): the nalmefene arm had a higher proportion of patients at lower drinking levels and lower proportions of patients at the higher drinking levels compared to PI.	ESENSE1 (Lundbeck, 2012b) ESENSE2 (Lundbeck, 2012c) SENSE (Lundbeck, 2012a)

Factor	Chosen values	Justification	Reference
Cycle length	1 month (28 days) for short term 1 year for long term	A 1-month (28-day) cycle length was applied to be aligned with the phase 3 nalmefene clinical studies trials' patient follow-up (TAC over 28 days; number of HDDs over 28 days) and with common clinical management. For the long-term phase, a 1-year cycle length was applied. The availability of reliable clinical data allowed for the application of a 1-year cycle length, particularly with regard to (1) the available evidence for the maintenance of effect and probability of recurrence of heavy drinking after initial response to the treatment by patients and (2) the available evidence of efficacy for the second-line treatment option to which patients are directed if their initial treatment with nalmefene + PI or PI has failed (assisted withdrawal followed by naltrexone or acamprosate + PI). A 1-year cycle length also reduces the number of assumptions needed, allowing a limited number of simple assumptions after the trial period. Additionally, the simple approach taken is believed to limit as far as possible the uncertainty related to the extrapolation of the outcomes from the phase 3 studies.	ESENSE1 (Lundbeck, 2012b) ESENSE2 (Lundbeck, 2012c) SENSE (Lundbeck, 2012a) Barbosa et al., 2010 Taylor et al., 1985
Half-cycle correction	Not included	Due to the initial model using monthly cycles, the incorporation of half-cycle correction were seen to be negligible, in line with published recommendations.	Barendregt, 2009
Were health effects measured in QALYs; if not, what was used?	Yes	The utilities, in combination with time spent in each health state plus mortality, were derived for the base-case analysis from the area under the curve for the ESENSE1, ESENSE2, and SENSE trials to compute the QALYs over 1 year for each treatment. The area under the curve captured the effect of improved utility due to reduced DRLs, but also the potential disabilities from nalmefene side effects. The utilities were derived from EQ-5D using the UK tariff in line with NICE reference case. For years 2 to 5 of the base-case analysis, the pooled utilities from nalmefene trials were used for high/very high-risk, medium-risk, and low-risk/abstinent groups. For the alcohol-attributable harmful events, except for utility for respiratory infection (year 1-5), utilities were derived from the Sheffield Alcohol Policy Model (2009). The utilities used in the Sheffield Alcohol Policy Model were derived from a single source, the Health Outcomes Data Repository (2008), to avoid potential bias and variability between studies. The Health Outcomes Data Repository data measure utilities using the EQ-5D as recommended by NICE for health economic evaluations in a UK population	ESENSE1 (Lundbeck, 2012b) ESENSE2 (Lundbeck, 2012c) SENSE (Lundbeck, 2012a) Sheffield Alcohol Policy Model (Sheffield University, 2009 Sisk et al., 2003

Factor	Chosen values	Justification	Reference
		of 424,000. For respiratory infection, utility reported in a publication by Sisk and colleagues (2003) was used.	
Discount of 3.5% for utilities and costs	Yes	Costs and outcomes are discounted at a default annual rate that is set to 3.5% for costs and outcomes, in line with recommendations set by NICE	NICE, 2013
Perspective of cost	NHS + PSS and societal cost in a sensitivity scenario	The model takes the perspective of the NHS in England and Wales to analyse healthcare costs; societal costs are included in the model. This is in line with the final scope and recommendations set by NICE. All costs are inflated to 2012 costs (PSSRU costs 2011/2012)	NICE, 2013
NHS = National Health Service; NICE = UK National Institute for Health and Clinical Excellence; PSS = Personal Social Services; PSSRU = Personal Social Services Research Unit; QALYs = quality-adjusted life-years.			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in Sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

(i) Nalmefene in conjunction with psychosocial intervention

Psychosocial support is the mainstay of treatment for alcohol dependence and has been shown to be effective in reducing alcohol consumption (NICE, 2011a). Nalmefene plus psychosocial support is the intervention under consideration, compared with psychosocial support alone in actively drinking patients (high DRL or above) who do not require immediate assisted alcohol withdrawal. This is in accordance with the marketing authorisation for nalmefene.

Consequently, PI is used as the main comparator for nalmefene therapy in the reduction of alcohol consumption in alcohol-dependent patients.

(ii) Other pharmacological agents

As stated in Section 2.7, there are currently no pharmacological treatments other than nalmefene licensed in the UK or Europe for the reduction of alcohol consumption in alcohol-dependent patients. Three other pharmacological agents have been approved for the management of alcohol dependence: disulfiram, acamprosate, and naltrexone. These treatments are indicated as adjunctive to psychosocial support, with maintenance of abstinence and relapse prevention being the treatment goal, and are prescribed to patients who have reached abstinence following an alcohol withdrawal/detoxification process (NICE, 2011a).

In contrast to these drugs and treatment goals, nalmefene is indicated for reduction of alcohol consumption in patients with alcohol dependence. Nalmefene can specifically be prescribed to actively drinking patients and does not require an assisted alcohol withdrawal process before being used. Moreover, the evidence assessing naltrexone outside of its indication and in the same context as nalmefene for the treatment of actively drinking alcohol-dependent patients is very limited. From the available evidence, the efficacy of naltrexone in the reduction of alcohol consumption could not be quantified and is inconclusive (Section 2.7 and Section 6.7). Moreover, as described in Section 6.7.4, undertaking an indirect comparison aligned with the NICE guidelines/reference case was not possible. Therefore, no pharmacological agent is considered as a relevant comparator for nalmefene in the reduction of alcohol consumption in patients with alcohol dependence.

However, in order to fully reflect the scope of this technology appraisal and in line with NICE CG115 (which recommends the unlicensed use of naltrexone or acamprosate in treatment of mild alcohol dependence only for patients for whom psychosocial intervention has failed), a secondary treatment option with

the use of naltrexone or acamprosate to maintain abstinence has been included in the model (see Figure B20).

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the “response” criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from nonresponders and other equity considerations.

The patient cohort begins in the model at a designated drinking level: high or very high DRL as per the indication for the use of nalmefene. From this initial drinking level, each patient can move among the ranges of drinking levels after each cycle (1 month) for the first year. After 12 months and up to year 5, the patients transition to one of three drinking states of 1-year cycle length (Section 7.2.4). Additionally, after every cycle, patients can move to an alcohol-attributable harmful-event health state in the model (see details in Section 7.2.4). The transition probabilities between all these health states are based on drinking levels and patterns taken from the nalmefene clinical trials (directly applied for the first year of the model) and in conjunction with assumptions and additional evidence after 1 year (Section 7.3.2).

The EMA guidelines proposed as clinically relevant a response definition of a two-category downward shift in WHO risk levels of drinking (i.e., change from baseline of very high risk to at least medium risk or from high risk to at least low risk) (EMA, 2010). This reduction in alcohol consumption is believed to translate into clinically relevant improvements in health outcomes on an individual patient level (EMA, 2010) (Section 6.3). This was the basis for the different responder definitions used in the studies (Section 6.3.5) and also for the model.

Therefore, in the model, for the nalmefene strategy and the psychosocial intervention strategies after the initial 12 months of treatment (within-trial time

horizon of the model), patients being at low-risk drinking level or abstinent at 1 year were considered to be controlled drinkers (having fully responded to treatment and thus discontinued treatment). To these same patients, a yearly risk of relapse to high or very high DRL and to treatment was applied, as described in Section 7.2.4. Patients at medium DRL after the initial 12 months of treatment were considered having partially responded to treatment and continued treatment until they moved either to controlled drinking or to high or very high drinking. Finally, the patient cohort that is in the high or very high-risk drinking level after 12 months (viewed as nonresponders) is modelled to discontinue current treatment and change treatment strategy to an abstinence-orientated approach, which includes assisted alcohol withdrawal followed by acamprosate or oral naltrexone + PI for relapse prevention.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (Section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Nalmefene is expected to be used for the reduction of alcohol consumption in alcohol-dependent patients who continue to have a high drinking risk level 2 weeks after initial assessment. In the context of the nalmefene pivotal clinical trials, as described in Sections 6.3.7, 6.5.3, and 6.10.2, a sizeable proportion of patients considerably reduced their alcohol consumption in the period (1-2 weeks) between screening and randomisation. Nalmefene is not indicated for this group of patients. The economic analysis presented here starts when nalmefene is prescribed from the point of randomisation. In the phase 3 nalmefene trials described in Sections 6.2 to 6.5, patients who had reduced alcohol consumption after screening, but prior to treatment with nalmefene, had not been randomised; thus the effect during this period cannot be determined specifically for compared arms and was assumed to be equal and the effect nullified between compared cohorts.

For the short-term (1-year) phase, pooled data from the ESENSE1 and ESENSE2 trials (6-month trials) and the SENSE trial (12-month trial) have been used to derive the monthly transition probabilities between the five different drinking levels in the model, to which the risk for alcohol-attributable harmful events was applied (Section 7.3.2).

For the long-term (up to 5 years) phase, the following data and assumptions are used for the different health states:

- The proportions of patients who are in the high- and very high-risk drinking levels at 12 months remain in these states, except for alcohol-attributable harmful events, for the entire phase (based on the responder analysis

proposed by the EMA and the conservative assumption that the patient keeps drinking at a high level until the end of the model (Section 7.2.7)

- The transition probabilities from the medium-risk drinking level (with continuous nalmefene + PI treatment) to controlled drinking or high and very high drinking were derived from the average transition probabilities of the medium-risk drinking level for the last 6 months in the SENSE 12-month trial (Section 7.3.2). This was judged to be the most appropriate approach to make use of the evidence collected on long-term drinking levels, only accounting for shifts in drinking level of people who have stabilised on treatment with nalmefene.

- For the controlled-drinking state, the probability of relapse is incorporated in our model in a similar manner as seen in the model from Barbosa and colleagues (2010) (Section 7.3.2)

- For the 1-year time horizon model, pooled data from the ESENSE1, ESENSE2, and SENSE trials were used to model the monthly risk of nalmefene adverse events leading to nalmefene withdrawal (Section 7.2.4 and Section 6.4.3) and to model the monthly risk of nonnalmefene-related withdrawal reasons (Appendix 16).

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Short-term health states (first year)

As mentioned in Section 7.2.1, for the short-term (1-year) phase, pooled data from ESENSE1, ESENSE2, and SENSE have been used to derive the monthly transition probabilities between the five drinking levels in the model. The monthly transition probabilities were based on the count of patients (observed cases) each month in each WHO health state from the three pooled nalmefene trials. To each of these monthly health states, the risk for alcohol-attributable harmful events was applied. The monthly transition probabilities between drinking levels can be found in Appendix 16. Even the transition probabilities for dropping out due to adverse events from nalmefene or due to other reasons were modelled based on the count of patients (observed cases) each month in each WHO health state from the three pooled nalmefene trials and can be found in Appendix 16.

Long-term health states (2-5 years)

Controlled-drinking

For the controlled-drinking state, the probability of relapse is incorporated in our model in a similar manner as seen in the model from Barbosa and colleagues (2010) appraising drinking patterns. Barbosa and colleagues based their transition probabilities between drinking states after treatment on data from a study performed by Taylor and colleagues (1985). In the Taylor study, researchers followed patients for 10 years and monitored the patients'

risks of relapsing to drinking after being admitted into a controlled study of treatment versus advice with a 1- and 2-year follow-up. In this study, the authors defined three levels of drinking:

- Troubled drinking, defined as meeting any of these criteria: “drinking more than five pints of beer or their alcohol equivalent on any day during the month OR experiencing any dependence symptoms OR experiencing other adverse consequences”

- Light social drinking, defined as “drinking, but never more than five pints of beer, or their alcohol equivalent, in any day of the week; for at least three successive months without experiencing dependence symptoms or other adverse consequences”

- Complete abstinence from alcoholic beverage, or any scattered, trivial drinking not covered in the troubled drinking or light social drinking levels. For example, drinking less than five pints occasionally, but not frequently enough to count as light social drinking.

Over the 10 years of follow-up, the Taylor and colleagues (1985) monitored the drinking stability over time to predict the proportion of patients that retain the same drinking status for the following year. In the current model, the drinking stability for abstinent patients was used to model the risk of relapse for patients in the controlled-drinking state. This was a conservative choice of estimate considering that “light social drinking” patients were stable at this state for 86% as compared with 81% for “abstinent” patients.

The article by Taylor and colleagues (1985) did not report the effect of present consumption on the following year’s consumption. Thus, in this analysis, when patients relapsed from the controlled-drinking state, an assumption was made that they did so to heavy drinking (high or very high WHO DRL), with the same proportions as the initial population in the model. These patients are then routed back to their original treatment with nalmefene + PI or PI as in the first year of treatment (phase 1 of the model).

Medium-risk drinking

For the medium-risk drinking level, the yearly transition probabilities from the medium-risk drinking level to controlled drinking or high and very high drinking were derived from the average transition probabilities of the medium-risk drinking level for the last 6 months in the SENSE 12-month trial. This was judged to be the most appropriate source of data in this context and was assessed as appropriate by the health economic and clinical experts which Lundbeck consulted. These transition probabilities are listed in Table B51.

Table B51. Transition probabilities from the medium-risk drinking level, years 2 through 5

Treatment	Males	Females
Nalmefene + psychosocial intervention		
Medium to very high and high	9%	8%

Treatment	Males	Females
Medium to controlled drinking	49%	40%
Medium to medium	42%	52%
Psychosocial intervention		
Medium to very high and high	16%	21%
Medium to controlled drinking	26%	43%
Medium to medium	58%	36%

High/very high-risk drinking and second-line treatment option

The effect of the second-line treatment was based on evidence on the effectiveness of assisted alcohol withdrawal followed by acamprosate or oral naltrexone + PI for relapse prevention was taken from the NICE clinical guideline 115 published in 2011, which aimed to evaluate the role of pharmacological interventions in the treatment of alcohol dependence. The guideline reviewed the published evidence and used a mixed-treatment comparison approach to assess effectiveness of acamprosate or oral naltrexone + PI for relapse prevention, using data from 32 RCTs, the mean probabilities of relapse to heavy drinking at 1 year for oral naltrexone and acamprosate. All trials included pharmacological treatments (acamprosate or oral naltrexone) as an adjunct to psychosocial treatment. The network meta-analysis showed that the probability of relapse to heavy drinking at 1 year was 0.8176 (95% CI 0.3894-0.9996) for acamprosate and 0.8253 (95% CI 0.4095-0.9997) for oral naltrexone. Due to the similar effectiveness of acamprosate and oral naltrexone, in the model, common effectiveness is assumed of the two drugs based on the results for acamprosate.

When patients have succeeded on treatment with naltrexone/acamprosate, they are transitioned to the abstinence health state (Figure B20). A yearly probability to resume drinking and to relapse to heavy drinking (high/very high-risk drinking) is then applied to this cohort of patients. This yearly probability of relapse was applied the same way as the recurrence to high/very high-risk drinking for the controlled drinking health state was applied: yearly probability of relapse to heavy drinking from abstinence of 19% (Taylor et al., 1985).

Patients who relapse to heavy drinking after successful abstinence treatment and patients who originally failed this abstinence approach (relapsed to heavy drinking during the year of treatment with naltrexone or acamprosate) can either revert to drinking at a high- or very high-risk level or receive a new round of abstinence treatment. In the model, the probability of going back to a new round of abstinence treatment has been set to 50% for both of groups (relapsing from abstinence or new round of treatment after failing treatment), based on expert opinion. Patients not going back to a new round of treatment continue to drink at high/very high drinking level until the next year and have a 50% probability once again of returning to abstinence treatment.

Calculation of the incidence of alcohol-attributable harmful events

A patient's risk of having an alcohol-attributable harmful event was modelled as the risk for the event by WHO levels of alcohol consumption. Injury and disease morbidity and mortality due to the alcohol-attributable conditions presented in Table B48 were modelled using a number of different steps and data sources, and employing recently developed methods (Rehm et al., 2008; Taylor et al., 2008).

The incorporation of the incidence of alcohol-attributable harmful events in the model used the following method:

$$\text{Personal Risk Disease (i)} = \text{Population Risk Disease (i)} \times \text{RRDisease(i)(x)}$$

Where *Personal Risk Disease (i)* is the risk of an event *i* for a time period; *RRDisease (i)(x)* is the relative risk of having the event *i* given alcohol consumption of *x*; and *Population Risk Disease (i)* is the risk of event *i* in the general population (including alcohol-attributable and nonalcohol-attributable events).

The incorporation of the incidence of alcohol-attributable harmful events in the model used the following steps:

Step 1: Calculation of the population risk of disease

Population Risk Disease (i) = Number of Events / Country Total Population

In this model, the Number of Events corresponds, for morbidity, to the number of yearly hospital admissions in the general population for a specific alcohol-attributable disease or injury included in the model (including alcohol-attributable and nonalcohol-attributable events). For mortality, both in the general population and for each of the diseases/injuries included in the model, death within 90 days of hospital admission was used. ICD-10 codes were used for this data collection (Table B52). These risks were calculated separately for males and females.

Country-specific data for England were collected, by sex for the number of deaths and episodes of hospital admissions, to model the morbidity and mortality according to the methods described using data from the Hospital Episode Statistics for England, Inpatient Statistics (Health and Social Care Information Centre, 2012) and the Deaths Registered in England and Wales, 2012 (ONS, 2013)[4] (Appendix 16).

[4] Sources of number of admissions for alcohol-attributable harmful events, except transport injuries and other injuries: (1) Health and Social Care Information Centre 2012, Hospital Episode Statistics for England – Inpatient Statistics, 2011-12: Primary diagnosis, 3 characters; and (2) Health and Social Care Information Centre 2012, Hospital Episode Statistics for England – Inpatient Statistics, 2011-12: Primary diagnosis, 4 characters.

Source of number of transport injuries and other injuries: Health and Social Care Information Centre 2012, Hospital Episode Statistics for England – Inpatient Statistics, 2011-12: External causes.

Source of number of deaths for alcohol-attributable harmful events except transport injuries and other injuries: Office for National Statistics 2013a, Deaths Registered in England and Wales, 2012 – Deaths: underlying cause, sex and age-group. Various chapters.

Source of number of deaths for transport injuries and other injuries: Office for National Statistics 2013a, Deaths Registered in England and Wales, 2012 – Deaths: underlying cause, sex and age-group.

Table B52. General population: annual probability of event

Condition	ICD-10 code
Morbidity[a]	
Ischaemic heart disease	I20-I25
Ischaemic stroke and other nonischaemic stroke	I60-I62
Haemorrhagic	I63-I66
Cirrhosis of the liver	K70, K74, K71.1
Acute and chronic pancreatitis	K85, K86.1
Lower respiratory infections	J10-J18, J20-J22
Motor vehicle accidents	See Footnote c
Injuries other than from transport	See Footnote d
Mortality[b]	
Ischaemic heart disease	I20-I25
Ischaemic stroke and other nonischaemic stroke	I60-I62
Haemorrhagic	I63-I66
Cirrhosis of the liver	K70, K74
Acute and chronic pancreatitis	K85
Lower respiratory infections	J10-J18, J20-J22
Motor vehicle accidents	See Footnote c
Injuries other than from transport	See Footnote d

Source: The Health and Social Care Information Centre (2012) and ONS (2013).

ICD-10 = International Classification of Diseases, 10th Revision.

[a] Based on number of inpatient admissions from the Hospital Episode Statistics for England (The Health and Social Care Information Centre, 2012).

[b] Based on number of Deaths Registered in England and Wales, 2012 (ONS, 2013)

[c] V021-V029, V031-V039, V041-V049, V092, V093, V123-V129, V133-V139, V143-V149, V194-V196, V203-V209, V213-V219, V223-V229, V233-V239, V243-V249,V253-V259, V263-V269, V273- V279, V283-V289, V294-V299, V304-V309, V314-V319, V324-V329, V334-V339, V344-V349, V354-V359, V364-V369, V374-V379, V384-V389, V394-V399, V404-V409, V414-V419, V424-V429, V434-V439, V444-V449, V454-V459, V464- V469, V474-V479, V484-V489, V494-V499, V504-V509, V514-V519, V524-V529, V534-V539, V544-V549, V554-V559, V564-V569, V574-V579, V584-V589, V594-V599, V604-V609, V614-V619, V624-V629, V634-V639, V644-V649, V654- V659, V664-V669, V674-V679, V684-V689, V694-V699, V704-V709, V714-V719, V724-V729, V734-V739, V744-V749, V754-V759, V764-V769, V774-V779, V784-V789, V794-V799, V803-V805, V811, V821, V830-V833, V840-V843, V850-V853, V860-V863, V870-V878, V892.

[d] X40-X49, W00-W19, X00-X09, W65-W74, rest of V-series, and W20-W64, W 75-W99, X10-X39, X50-X59, Y40-Y86, Y88, and Y89 (rest of V = V-series minus those listed in Footnote c), X60-X84 and Y87.0, X85-Y09, Y87.1.

Step 2: Calculation of the personal risk of disease

Personal Risk Disease was calculated using the RRDisease and multiplying this by the Population Risk Disease calculated in step 1.The equations used to calculate RRDisease according to the level of alcohol consumption (for morbidity and mortality) can be found in Appendix 16. These risk equations for RRDisease, as well as the approach described above, were developed independently by the Social and Epidemiological Research (SER) Department at the Centre for Addiction and Mental Health in Toronto, Canada. This method is recognised internationally as the standard for modelling the

incidence of alcohol-attributable harmful events and is used by the WHO for assessing the burden of alcohol (WHO, 2000).

Because some of the harmful events (morbidity and mortality) occur on the basis of immediate heavy drinking (immediate-drinking events) and others occur on the basis of continuous drinking (continuous-drinking events), different approaches were needed for each type.

The risk of the continuous-drinking events is associated with the average drinking level over time. Thus, the risk of these events was based on the average monthly drinking level (in grams per day) by WHO DRLs from the ESENSE1, ESENSE2, and SENSE trials (see Table B53 for year 1 and Table B54 for years 2 to 5). For phase 1 of the model (year 1), the risk of events was applied monthly. For phase 2 of the model (years 2 to 5), the risk of events was applied yearly.

The risk for the immediate-drinking events related to immediate heavy drinking is associated with the drinking level when drinking. Thus, the risk of these events was based on the drinking level (in grams per day) per HDD and the number of HDDs per month, by WHO DRLs, as seen in the ESENSE1, ESENSE2, and SENSE trials (see Table B53 for year 1 and Table B54 for years 2 to 5). For the days when the patient does not experience a HDD, the risk of the event for the general population is applied. The resulting relative risks and probabilities used in the model can be found in Appendix 16.

In line with earlier publications on harmful events from drinking (Rehm et al., 2011; Rehm et al., 2009), it was not realistic to assume that patients would experience increased risk of transport injuries and injuries other than transport for the entire day, because patients must be in a specific environment to experience the event. Thus, an adjustment of hours drinking per day was incorporated into the model's calculations for these events. In the analysis, the hours drinking per day and thus the time the patient has the risk of experiencing the event is set to 3 hours, in accordance with earlier publications (Rehm et al., 2011; Rehm et al., 2009).

Table B53. Drinking per DRL, Year 1

	Males	Females
Average consumption (g/day) per DRL		
Very high risk	134	94
High risk	78	50
Medium risk	50	29
Low risk	21	11
Abstinent	0	0
Consumption (g/day) per HDD		
Very high risk	153	108
High risk	113	74
Medium risk	107	67
Low risk	81	50
Abstinent	0	0
Number of HDDs per month per DRL		
Very high risk	25	24
High risk	19	19
Medium risk	10	9
Low risk	3	3
Abstinent	0	0
DRL = drinking-risk level; HDD = heavy drinking day.		

Table B54. Drinking per DRL, Years 2 through 5

	Males	Females
Average consumption (g/day) per DRL		
Very high + high risk	104	75
Medium risk	50	29
Controlled drinking	16	9
Consumption (g/day) per HDD		
Very high + high risk	132	93
Medium risk	107	67
Controlled drinking	65	40
Number of HDDs per month per DRL		
Very high + high risk	22	22
Medium risk	10	9
Controlled drinking	3	2
DRL = drinking-risk level; HDD = heavy drinking day.		

Death

Death from alcohol-attributable harmful events was modelled in the same way as the diseases/injuries themselves as explained above. Country-specific, all-cause, age-related mortality incorporated in the model has been retrieved from the Deaths Registered in England, 2012 (ONS, 2013).

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

For transition probabilities seen to vary over time, these where included with variation over time in the model. The main type of probabilities included with variation in the model was the treatment effect of nalmefene, as this was shown to vary with time (see Section 6.5.3 and Table B8 and Table B9). As mentioned in Section 7.2.1, for the short-term (1-year) phase, pooled data from ESENSE1, ESENSE2, and SENSE have been used to derive the monthly transition probabilities between the five drinking levels in the model. The monthly transition probabilities were based on the count of patients (observed cases) each month in each WHO health state from the three pooled nalmefene trials. Thus, these transition probabilities that are the main driver of the model vary with time as observed in the clinical trials. Other transition probabilities (e.g., risk of harmful events), however, do not vary with time, as they are related to the resulting drinking level of the patients and not seen to be dependent on when they occur.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Not applicable, as trial data were incorporated directly into the model.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The validity, internal and external, as well as the applicability of the evidence presented in the context of this submission, has been assessed, commented on, directed, and validated by multiple experts from the UK clinical, public health, and health economic fields. This has been performed in covering the different STA considerations, with a focus on the following components:

1. Nalmefene's place in therapy in England and Wales

Nalmefene's case has been discussed in context of the STA application with UK experts (including experts from England and Wales) of different and complementary perspectives: clinicians of different types in primary and secondary care, as well as public health experts. This was with regard to the NICE CG115. We are confident that Lundbeck has presented nalmefene in the STA with the appropriate position within the healthcare system for the clinical management of alcohol dependence.

2. The approach for systematically reviewed published evidence

For the review of naltrexone in reduction, published evidence and performed assessment of published evidence such by Cochrane and NICE CG115 have been discussed in the context of the STA with UK clinical experts in the treatment of alcohol dependence. The design and specific population of the naltrexone clinical trials of relevance to be compared with nalmefene trials have been emphasised, which guided the review protocol.

For the review of psychosocial interventions, again the NICE CG115 has been reviewed with regard to the scope of the STA. After the review factors related to the types of psychosocial intervention mentioned in the scope were discussed with clinical experts, the psychosocial intervention approaches used during the nalmefene clinical trials and recommended with the use of nalmefene in the SPC were also discussed. This perspective has been included in the review, in addition to the psychosocial interventions mentioned in the STA scope, all types of psychosocial interventions being proxies of BRENDA and the psychosocial intervention to be used with nalmefene, per the SPC.

3. The technical applicability of the nalmefene clinical trial outcomes to cost-effectiveness modelling

The technical applicability of the clinical trials outcomes for modelling in a valid way and in reflexion of the real-life situation has been validated in collaboration with UK epidemiological/public health, clinical, and health economic experts. After application of optimal and up-to-date technical modelling approaches, the external validation of the model results involved

different components, mainly (1) the external validity in terms of incremental reduction of drinking for compared treatment arms from the nalmefene clinical trials and (2) the external validity in terms of number of alcohol-attributable diseases, injuries, and deaths as computed by the model.

The first main external validity aspect was related to the incremental reduction of drinking for the two compared treatment arms of the nalmefene clinical trials. This was assessed with regards to the QALY difference between the two treatment arms. The amplitude of the QALY difference is relatively low. It was assessed and explained by the experts the following way:

- Generic quality of life measures like the EQ-5D are of limited sensitivity in alcohol dependence as concluded by Luquiens and colleagues (2012). There could be insufficient correlation between changes in drinking behaviour and alcohol consumption with patient-perceived impact on health status using this measure, which could have led to an underestimation of the QALY gains for nalmefene in this analysis.
- The EQ-5D was modelled based on observed case data from the nalmefene clinical trials (without the application of an imputation method for missing data). The use of an imputation method such as the mixed model repeated measures (MMRM) method would have increased the QALY difference.

The second main external validity was related to the number of alcohol-attributable diseases, injuries, and deaths computed by the model. The modelling work on this aspect was performed in close collaboration with the Social and Epidemiological Research Department of the Centre for Addiction and Mental Health in Toronto, Canada, led by Jürgen Rehm. This academic group assessed/evaluated the outcomes from the model, and found results to be aligned with their own public health assessments using a similar methodology. This approach provided additional validation of the comparative effectiveness modeled in terms of comparative reduction of drinking between nalmefene + PI and PI.

Finally, the quality-control procedures undertaken have been performed according with ISPOR good practice (Eddy et al., 2012).

4. The cost-effectiveness model applicability and alignment with the English context and with the NICE requirements

The applicability of the clinical trials outcomes has been assessed for its appropriateness in an English and Welsh setting by clinical experts. These experts have also led the development of the post-trials modelling components for their representation of the real-life practice in alignment with the recommendations from the NICE CG115. The best UK data available post-trials modelling having been used, and the assumptions needed to complement them were developed by clinical experts aiming for optimal representation of clinical practice.

5. Decision-problem meeting: NICE advice on the submission approach and related technical applicability

At the decision-problem meeting with NICE in December 2013, Lundbeck went through the approach of the development of the STA to gain feedback and advice from both methodological and technical viewpoints. This meeting provided reassurance and confidence to Lundbeck about the content of the current STA. Lundbeck believes this submission is fully aligned with the advice given by NICE during the decision-problem meeting.

6. Validation of the STA submission

When the STA submission was at final draft stage, three experts (in the fields of clinical management of alcohol dependence, public health, and health economics) validated the submission in terms of clinical and technical accuracy and best practice in evidence-based medicine, but also in context of the current practice and the place of nalmefene in the English and Welsh settings.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B55. Summary of variables applied in the economic model

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
General parameters				
Age	48	N/A	N/A	ESENSE1 & 2 and SENSE
Sex (% male)	69.0	N/A	N/A	ESENSE1 & 2 and SENSE
Discount rate: cost	3.50%	N/A	N/A; in line with NICE reference case	NICE, 2013
Discount rate: outcomes	3.50%	N/A	N/A; in line with NICE reference case	NICE, 2013
Proportion of day at risk of road traffic accident (hours)	3	N/A	N/A	Rehm and Scafato, 2011; Rehm et al., 2009
Proportion of day at risk of other accidents (hours)	3	N/A	N/A	Rehm and Scafato, 2011; Rehm et al., 2009
Proportion of visits to GP (to specialised care)	75%	N/A	N/A	Clinical experts, Section 7.3.5
Number of visits first month for nalmefene treatment	3.00	N/A	N/A; as specified in clinical trials	ESENSE1 & 2 and SENSE
Number of visits first month for PI treatment	3.00	N/A	N/A; as specified in clinical trials	ESENSE1 & 2 and SENSE
Medical visits per month, nalmefene	1.00	N/A	N/A; as specified in clinical trials	ESENSE1 & 2 and SENSE

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Medical visits per month for PI treatment	1.00	N/A	N/A; as specified in clinical trials	ESENSE1 & 2 and SENSE
Cost of nalmefene	£3.03	N/A	N/A	Section 1.10
General population probability of harmful event				
Males				
Heart disease	0.71%	0.000713[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Ischaemic stroke	0.15%	0.000146[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Haemorrhagic stroke	0.05%	0.000048[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Cirrhosis of the liver	0.06%	0.000055[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Pancreatitis	0.05%	0.000055[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Lower respiratory infection	0.56%	0.000564[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Road traffic accident	0.07%	0.000067[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Fall or other injury	2.33%	0.002334[a]	N/A; total population data	Health and Social Care Information Centre, 2012

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Females				
Heart disease	0.36%	0.000356[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Ischaemic stroke	0.15%	0.000147[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Haemorrhagic stroke	0.05%	0.000045[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Cirrhosis of the liver	0.03%	0.000031[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Pancreatitis	0.04%	0.000039[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Lower respiratory infection	0.52%	0.000518[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Road traffic accident	0.03%	0.000029[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Fall or other injury	2.29%	0.002295[a]	N/A; total population data	Health and Social Care Information Centre, 2012
Mortality, males				
Heart disease	0.144%	0.000144[a]	N/A; total population data	Office for National Statistics, 2013
Ischaemic stroke	0.030%	0.00003[a]	N/A; total population data	Office for National Statistics, 2013

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Haemorrhagic stroke	0.014%	0.000014[a]	N/A; total population data	Office for National Statistics, 2013
Cirrhosis of the liver	0.016%	0.000016[a]	N/A; total population data	Office for National Statistics, 2013
Pancreatitis	0.002%	0.000002[a]	N/A; total population data	Office for National Statistics, 2013
Lower respiratory infection	0.044%	0.000044[a]	N/A; total population data	Office for National Statistics, 2013
Road traffic accident	0.003%	0.000003[a]	N/A; total population data	Office for National Statistics, 2013
Fall or other injury	0.035%	0.000035[a]	N/A; total population data	Office for National Statistics, 2013
Mortality, females				
Heart disease	0.099%	0.000099[a]	N/A; total population data	Office for National Statistics, 2013
Ischaemic stroke	0.047%	0.000047[a]	N/A; total population data	Office for National Statistics, 2013
Haemorrhagic stroke	0.017%	0.000017[a]	N/A; total population data	Office for National Statistics, 2013
Cirrhosis of the liver	0.009%	0.000009[a]	N/A; total population data	Office for National Statistics, 2013
Pancreatitis	0.002%	0.000002[a]	N/A; total population data	Office for National Statistics, 2013
Lower respiratory infection	0.058%	0.000058[a]	N/A; total population data	Office for National Statistics, 2013
Road traffic accident	0.001%	0.000001[a]	N/A; total population data	Office for National Statistics, 2013
Fall or other injury	0.022%	0.000022[a]	N/A; total population data	Office for National Statistics, 2013

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Average consumption (g/day) per DRL				
Males				
Very high risk	134	1.523	Gamma(7700,0.017)	ESENSE1 & 2 and SENSE
High risk	78	0.411	Gamma(35700,0.002)	ESENSE1 & 2 and SENSE
Medium risk	50	0.235	Gamma(44675,0.001)	ESENSE1 & 2 and SENSE
Low risk	21	0.331	Gamma(3947,0.005)	ESENSE1 & 2 and SENSE
Females				
Very high risk	94	1.974	Gamma(2276,0.041)	ESENSE1 & 2 and SENSE
High risk	50	0.387	Gamma(16493,0.003)	ESENSE1 & 2 and SENSE
Medium risk	29	0.278	Gamma(11207,0.003)	ESENSE1 & 2 and SENSE
Low risk	11	0.301	Gamma(1391,0.008)	ESENSE1 & 2 and SENSE
Consumption (g/day) per HDD				
Males				
Very high risk	153	2.302	Gamma(4401,0.035)	ESENSE1 & 2 and SENSE
High risk	113	1.500	Gamma(5654,0.02)	ESENSE1 & 2 and SENSE
Medium risk	107	1.845	Gamma(3354,0.032)	ESENSE1 & 2 and SENSE
Low risk	81	1.673	Gamma(2346,0.035)	ESENSE1 & 2 and SENSE

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Females				
Very high risk	108	2.369	Gamma(2095,0.052)	ESENSE1 & 2 and SENSE
High risk	74	1.406	Gamma(2741,0.027)	ESENSE1 & 2 and SENSE
Medium risk	67	1.253	Gamma(2854,0.023)	ESENSE1 & 2 and SENSE
Low risk	50	1.864	Gamma(707,0.07)	ESENSE1 & 2 and SENSE
Number of HDDs per month per DRL				
Males				
Very high risk	25	0.193	Gamma(16826,0.001)	ESENSE1 & 2 and SENSE
High risk	19	0.211	Gamma(8136,0.002)	ESENSE1 & 2 and SENSE
Medium risk	10	0.137	Gamma(5298,0.002)	ESENSE1 & 2 and SENSE
Low risk	3	0.085	Gamma(1581,0.002)	ESENSE1 & 2 and SENSE
Females				
Very high risk	24	0.207	Gamma(13929,0.002)	ESENSE1 & 2 and SENSE
High risk	19	0.344	Gamma(2900,0.006)	ESENSE1 & 2 and SENSE
Medium risk	9	0.208	Gamma(1929,0.005)	ESENSE1 & 2 and SENSE
Low risk	3	0.126	Gamma(474,0.006)	ESENSE1 & 2 and SENSE

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Nalmefene intake per month				
Males				
Very high risk	20	0.637	Gamma(1033,0.02)	ESENSE1 & 2 and SENSE
High risk	20	0.433	Gamma(2113,0.009)	ESENSE1 & 2 and SENSE
Medium risk	17	0.444	Gamma(1385,0.012)	ESENSE1 & 2 and SENSE
Low risk	14	0.321	Gamma(1880,0.007)	ESENSE1 & 2 and SENSE
Abstinence	9	0.972	Gamma(82,0.107)	ESENSE1 & 2 and SENSE
Females				
Very high risk	19	0.830	Gamma(531,0.036)	ESENSE1 & 2 and SENSE
High risk	19	0.765	Gamma(609,0.031)	ESENSE1 & 2 and SENSE
Medium risk	16	0.630	Gamma(683,0.024)	ESENSE1 & 2 and SENSE
Low risk	15	0.631	Gamma(552,0.027)	ESENSE1 & 2 and SENSE
Abstinence	8	1.497	Gamma(27,0.291)	ESENSE1 & 2 and SENSE
Cost parameters				
Cost of visit to GP	£63	13[b]	Gamma(25,2.52)	PSSRU, 2012
Cost of first attendance to specialised care	£94	19[b]	Gamma(25,3.76)	PSSRU, 2012
Cost of follow-up attendance to specialised care	£94	19[b]	Gamma(25,3.76)	PSSRU, 2012

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Cost of heart disease	£2,491	498[b]	Gamma(25,99.658)	Calculated from Sheffield University, 2009 (Appendices)
Cost of ischaemic stroke	£4,088	818[b]	Gamma(25,163.525)	Calculated from Sheffield University, 2009 (Appendices)
Cost of haemorrhagic stroke	£5,799	1160[b]	Gamma(25,231.956)	Calculated from Sheffield University, 2009 (Appendices)
Cost of cirrhosis of the liver	£3,750	750[b]	Gamma(25,150.008)	Calculated from Sheffield University, 2009 (Appendices)
Cost of pancreatitis	£4,373	875[b]	Gamma(25,174.903)	Calculated from Sheffield University, 2009 (Appendices)
Cost of lower respiratory infection	£2,999	600[b]	Gamma(25,119.974)	NHS Reference Costs 2011-12
Cost of transport injury	£5,468	1094[b]	Gamma(25,218.733)	Calculated from Sheffield University, 2009 (Appendices)
Cost of other injury	£5,296	1059[b]	Gamma(25,211.84)	Calculated from Sheffield University, 2009 (Appendices)
Utility parameters				
Utility per DRL from ESENSE and SENSE				
Very high and high risk	0.79	0.010	Beta(1310,348)	ESENSE1 & 2 and SENSE
Medium risk	0.82	0.010	Beta(1210,266)	ESENSE1 & 2 and SENSE

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Low risk and abstinence	0.86	0.010	Beta(1035,168)	ESENSE1 & 2 and SENSE
Utility from area under the curve				
Area under the curve from ESENSE and SENSE, nalmefene	0.83	Composite of the 5 parameters below		ESENSE1 & 2 and SENSE
Baseline	0.79	0.015	Beta(622,169)	ESENSE1 & 2 and SENSE
12 weeks	0.82	0.012	Beta(916,202)	ESENSE1 & 2 and SENSE
24 weeks	0.83	0.012	Beta(804,164)	ESENSE1 & 2 and SENSE
36 weeks	0.84	0.019	Beta(301,57)	ESENSE1 & 2 and SENSE
52 weeks	0.87	0.016	Beta(374,58)	ESENSE1 & 2 and SENSE
Area under the curve from ESENSE and SENSE, PI	0.81	Composite of the 5 parameters below		ESENSE1 & 2 and SENSE
Baseline	0.79	0.016	Beta(491,133)	ESENSE1 & 2 and SENSE
12 weeks	0.80	0.013	Beta(740,187)	ESENSE1 & 2 and SENSE
24 weeks	0.81	0.014	Beta(673,153)	ESENSE1 & 2 and SENSE
36 weeks	0.83	0.031	Beta(120,25)	ESENSE1 & 2 and SENSE
52 weeks	0.84	0.026	Beta(172,33)	ESENSE1 & 2 and SENSE
Utility of harmful events				
Utility, general population (used for adjustment)	0.85	0.026	Beta(164,28)	Sheffield University, 2009 (Appendices)

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Utility, heart disease	0.64	0.020	Beta(368,204)	Sheffield University, 2009 (Appendices)
Utility, ischaemic stroke	0.56	0.020	Beta(346,267)	Sheffield University, 2009 (Appendices)
Utility, haemorrhagic stroke	0.66	0.020	Beta(369,193)	Sheffield University, 2009 (Appendices)
Utility, cirrhosis of the liver	0.49	0.020	Beta(308,315)	Sheffield University, 2009 (Appendices)
Utility, pancreatitis	0.45	0.020	Beta(276,341)	Sheffield University, 2009 (Appendices)
Utility, lower respiratory tract infections	0.20	0.020	Beta(80,320)	Sheffield University, 2009 (Appendices)
Utility, transport injuries	0.60	0.020	Beta(359,241)	Sheffield University, 2009 (Appendices)
Utility, injuries other than transport	0.59	0.020	Beta(357,246)	Sheffield University, 2009 (Appendices)
Parameters for relative risk of harmful events[c]				
Male RR, ischaemic heart disease	0.98	0.269	Normal	Shield, 2011
Male RR, ischaemic stroke	0.98	0.269	Normal	Shield, 2011
Male RR, haemorrhagic stroke	0.77	0.157	Normal	Shield, 2011
Male RR, cirrhosis of the liver				
Beta 1	1.69	0.190	Normal	Shield, 2011
Beta 2	1.11	0.268	Normal	Shield, 2011
Male RR, pancreatitis	1.50	0.171	Normal	Shield, 2011
Male RR, lower respiratory infection	0.48	0.192	Normal	Shield, 2011

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Male RR, transport injury				
Beta 1	9.12	0.912[a]	N/A	Shield, 2011
Beta 2	3.29	0.329[a]	N/A	Shield, 2011
Beta 3	0.21	0.021[a]	N/A	Shield, 2011
Male RR, other injury	2.19	0.250	Normal	Shield, 2011
Female RR, ischaemic heart disease	0.98	0.269	Normal	Shield, 2011
Female RR, ischaemic stroke	0.98	0.269	Normal	Shield, 2011
Female RR, haemorrhagic stroke				
Beta 1	0.94	0.257	Normal	Shield, 2011
Beta 2	0.94	0.176	Normal	Shield, 2011
Female RR, cirrhosis of the liver				
Beta 1	2.35	0.224	Normal	Shield, 2011
Beta 2	0.90	0.320	Normal	Shield, 2011
Female RR, pancreatitis	1.50	0.171	Normal	Shield, 2011
Female RR, lower respiratory infection	0.48	0.192	Normal	Shield, 2011
Female RR, transport injury				
Beta 1	70.20	7.02[a]	N/A	Shield, 2011
Beta 2	3.29	0.329[a]	N/A	Shield, 2011
Beta 3	1.61	0.161[a]	N/A	Shield, 2011
Female RR, other injury	2.19	0.250	Normal	Shield, 2011
Male RR, mortality, haemorrhagic stroke	0.69	0.114	Normal	Shield, 2011
Male RR, mortality, cirrhosis of the liver	1.69	0.190	Normal	Shield, 2011
Female RR, mortality haemorrhagic stroke	1.47	0.354	Normal	Shield, 2011
Female RR, mortality, cirrhosis of the liver	2.35	0.224	Normal	Shield, 2011
Probability of relapse	0.19	0.047	Beta(13,55)	Taylor et al., 1985

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Transition probabilities between drinking levels and drop outs	Appendix 16	N/A	Dirichlet	ESENSE1 & 2 and SENSE
Parameters for secondary abstinence treatment				
Cost of assisted withdrawal	£1,044	209[b]	Normal	NICE 2011a
Cost of relapse prevention programme	£1,172	234[b]	Normal	NICE 2011a
Cost of relapse prevention programme, subsequent years	£1,172	234[b]	Normal	NICE 2011a
Secondary treatment effect	81.8%	0.156	Normal	National Collaborating Centre for Mental Health, 2011
Proportion having new treatment following relapse	50.0%	0.05[a]	Normal	Clinical experts, Section 7.3.5
Proportion drinking at high and very high levels having new treatment	50.0%	0.05[a]	Normal	Clinical experts, Section 7.3.5
Parameter for societal perspective				
Males				
Male causing death by dangerous driving rate	0.00001	0.000003[b]	Beta(264,19288400)	Sheffield University, 2009 (Appendices)
Male causing death by dangerous driving slope parameter	0.02928	0.005856[b]	Gamma(25,0.00117)	Sheffield University, 2009 (Appendices)
Male more serious wounding rate	0.00089	0.000178[b]	Beta(17136,19288400)	Sheffield University, 2009 (Appendices)
Male more serious wounding slope parameter	0.02047	0.004093[b]	Gamma(25,0.00082)	Sheffield University, 2009 (Appendices)
Male less serious wounding rate	0.10720	0.02144[b]	Beta(2067698,19288400)	Sheffield University, 2009 (Appendices)
Male less serious wounding slope parameter	0.02047	0.004093[b]	Gamma(25,0.00082)	Sheffield University, 2009 (Appendices)

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Male assault on a constable rate	0.00478	0.000957[b]	Beta(92262,19288400)	Sheffield University, 2009 (Appendices)
Male assault on a constable slope parameter	0.03638	0.007275[b]	Gamma(25,0.00146)	Sheffield University, 2009 (Appendices)
Male assault without injury rate	0.04554	0.009107[b]	Beta(878327,19288400)	Sheffield University, 2009 (Appendices)
Male assault without injury slope parameter	0.03638	0.007275[b]	Gamma(25,0.00146)	Sheffield University, 2009 (Appendices)
Male criminal damage rate	0.13088	0.026175[b]	Beta(2524395,19288400)	Sheffield University, 2009 (Appendices)
Male criminal damage slope parameter	0.07469	0.014938[b]	Gamma(25,0.00299)	Sheffield University, 2009 (Appendices)
Male theft from a person rate	0.01292	0.002583[b]	Beta(249137,19288400)	Sheffield University, 2009 (Appendices)
Male theft from a person slope parameter	0.00168	0.000336[b]	Gamma(25,0.00007)	Sheffield University, 2009 (Appendices)
Male robbery rate	0.01016	0.002033[b]	Beta(196024,19288400)	Sheffield University, 2009 (Appendices)
Male robbery slope parameter	0.00168	0.000336[b]	Gamma(25,0.00007)	Sheffield University, 2009 (Appendices)
Male robbery (business) rate	0.00095	0.00019[b]	Beta(18280,19288400)	Sheffield University, 2009 (Appendices)
Male robbery (business) slope parameter	0.00168	0.000336[b]	Gamma(25,0.00007)	Sheffield University, 2009 (Appendices)
Male burglary in a dwelling rate	0.01914	0.003829[b]	Beta(369264,19288400)	Sheffield University, 2009 (Appendices)
Male burglary in a dwelling slope parameter	0.00168	0.000336[b]	Gamma(25,0.00007)	Sheffield University, 2009 (Appendices)
Male burglary not in a dwelling rate	0.02062	0.004123[b]	Beta(397669,19288400)	Sheffield University, 2009 (Appendices)

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Male burglary not in a dwelling slope parameter	0.00168	0.000336[b]	Gamma(25,0.00007)	Sheffield University, 2009 (Appendices)
Male theft of a pedal cycle rate	0.00973	0.001945[b]	Beta(187621,19288400)	Sheffield University, 2009 (Appendices)
Male theft of a pedal cycle slope parameter	0.00168	0.000336[b]	Gamma(25,0.00007)	Sheffield University, 2009 (Appendices)
Male theft from vehicle rate	0.03441	0.006881[b]	Beta(663633,19288400)	Sheffield University, 2009 (Appendices)
Male theft from vehicle slope parameter	0.00860	0.00172[b]	Gamma(25,0.00034)	Sheffield University, 2009 (Appendices)
Male aggravated vehicle taking rate	0.00032	0.000064[b]	Beta(6179,19288400)	Sheffield University, 2009 (Appendices)
Male aggravated vehicle taking slope parameter	0.00860	0.00172[b]	Gamma(25,0.00034)	Sheffield University, 2009 (Appendices)
Male theft of vehicle rate	0.00535	0.001071[b]	Beta(103256,19288400)	Sheffield University, 2009 (Appendices)
Male theft of vehicle slope parameter	0.00860	0.00172[b]	Gamma(25,0.00034)	Sheffield University, 2009 (Appendices)
Male other theft rate	0.03543	0.007086[b]	Beta(683343,19288400)	Sheffield University, 2009 (Appendices)
Male other theft slope parameter	0.00168	0.000336[b]	Gamma(25,0.00007)	Sheffield University, 2009 (Appendices)
Male theft from shops rate	0.84053	0.168107[b]	Beta(16212536,19288400)	Sheffield University, 2009 (Appendices)
Male theft from shops slope parameter	0.00168	0.000336[b]	Gamma(25,0.00007)	Sheffield University, 2009 (Appendices)
Male violent disorder rate	0.00009	0.000018[b]	Beta(1779,19288400)	Sheffield University, 2009 (Appendices)
Male violent disorder slope parameter	0.02928	0.005856[b]	Gamma(25,0.00117)	Sheffield University, 2009 (Appendices)

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Male sexual offences rate	0.01049	0.002097[b]	Beta(202249,19288400)	Sheffield University, 2009 (Appendices)
Male sexual offences slope parameter	0.02928	0.005856[b]	Gamma(25,0.00117)	Sheffield University, 2009 (Appendices)
Male homicide rate	0.00004	0.000008[b]	Beta(778,19288400)	Sheffield University, 2009 (Appendices)
Male homicide slope parameter	0.02928	0.005856[b]	Gamma(25,0.00117)	Sheffield University, 2009 (Appendices)
Females				
Female causing death by dangerous driving rate	0.000003	0.000001[b]	Beta(55,20483300)	Sheffield University, 2009 (Appendices)
Female causing death by dangerous driving slope parameter	0.06583	0.013167[b]	Gamma(25,0.00263)	Sheffield University, 2009 (Appendices)
Female more serious wounding rate	0.00014	0.000029[b]	Beta(2965,20483300)	Sheffield University, 2009 (Appendices)
Female more serious wounding slope parameter	0.09664	0.019329[b]	Gamma(25,0.00387)	Sheffield University, 2009 (Appendices)
Female less serious wounding rate	0.01747	0.003493[b]	Beta(357786,20483300)	Sheffield University, 2009 (Appendices)
Female less serious wounding slope parameter	0.09664	0.019329[b]	Gamma(25,0.00387)	Sheffield University, 2009 (Appendices)
Female assault on a constable rate	0.00078	0.000156[b]	Beta(15964,20483300)	Sheffield University, 2009 (Appendices)
Female assault on a constable slope parameter	0.04369	0.008737[b]	Gamma(25,0.00175)	Sheffield University, 2009 (Appendices)
Female assault without injury rate	0.00742	0.001484[b]	Beta(151982,20483300)	Sheffield University, 2009 (Appendices)
Female assault without injury slope parameter	0.04369	0.008737[b]	Gamma(25,0.00175)	Sheffield University, 2009 (Appendices)

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Female criminal damage rate	0.01325	0.002649[b]	Beta(271313,20483300)	Sheffield University, 2009 (Appendices)
Female criminal damage slope parameter	0.12785	0.025569[b]	Gamma(25,0.00511)	Sheffield University, 2009 (Appendices)
Female theft from a person rate	0.00437	0.000874[b]	Beta(89504,20483300)	Sheffield University, 2009 (Appendices)
Female theft from a person slope parameter	0.00272	0.000544[b]	Gamma(25,0.00011)	Sheffield University, 2009 (Appendices)
Female robbery rate	0.00053	0.000105[b]	Beta(10804,20483300)	Sheffield University, 2009 (Appendices)
Female robbery slope parameter	0.00272	0.000544[b]	Gamma(25,0.00011)	Sheffield University, 2009 (Appendices)
Female robbery (business) rate	0.00005	0.00001[b]	Beta(1008,20483300)	Sheffield University, 2009 (Appendices)
Female robbery (business) slope parameter	0.00272	0.000544[b]	Gamma(25,0.00011)	Sheffield University, 2009 (Appendices)
Female burglary in a dwelling rate	0.00104	0.000207[b]	Beta(21222,20483300)	Sheffield University, 2009 (Appendices)
Female burglary in a dwelling slope parameter	0.00272	0.000544[b]	Gamma(25,0.00011)	Sheffield University, 2009 (Appendices)
Female burglary not in a dwelling rate	0.00112	0.000223[b]	Beta(22854,20483300)	Sheffield University, 2009 (Appendices)
Female burglary not in a dwelling slope parameter	0.00272	0.000544[b]	Gamma(25,0.00011)	Sheffield University, 2009 (Appendices)
Female theft of a pedal cycle rate	0.00329	0.000658[b]	Beta(67405,20483300)	Sheffield University, 2009 (Appendices)
Female theft of a pedal cycle slope parameter	0.00272	0.000544[b]	Gamma(25,0.00011)	Sheffield University, 2009 (Appendices)
Female theft from vehicle rate	0.01164	0.002328[b]	Beta(238415,20483300)	Sheffield University, 2009 (Appendices)

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Female theft from vehicle slope parameter	0.25754	0.051509[b]	Gamma(25,0.0103)	Sheffield University, 2009 (Appendices)
Female aggravated vehicle taking rate	0.00011	0.000022[b]	Beta(2219,20483300)	Sheffield University, 2009 (Appendices)
Female aggravated vehicle taking slope parameter	0.25754	0.051509[b]	Gamma(25,0.0103)	Sheffield University, 2009 (Appendices)
Female theft of vehicle rate	0.00181	0.000362[b]	Beta(37096,20483300)	Sheffield University, 2009 (Appendices)
Female theft of vehicle slope parameter	0.25754	0.051509[b]	Gamma(25,0.0103)	Sheffield University, 2009 (Appendices)
Female other theft rate	0.01199	0.002397[b]	Beta(245497,20483300)	Sheffield University, 2009 (Appendices)
Female other theft slope parameter	0.00272	0.000544[b]	Gamma(25,0.00011)	Sheffield University, 2009 (Appendices)
Female theft from shops rate	0.13696	0.027392[b]	Beta(2805354,20483300)	Sheffield University, 2009 (Appendices)
Female theft from shops slope parameter	0.00272	0.000544[b]	Gamma(25,0.00011)	Sheffield University, 2009 (Appendices)
Female violent disorder rate	0.00001	0.000003[b]	Beta(271,20483300)	Sheffield University, 2009 (Appendices)
Female violent disorder slope parameter	0.06583	0.013167[b]	Gamma(25,0.00263)	Sheffield University, 2009 (Appendices)
Female sexual offences rate	0.00000	0.000000[b]	Beta(0,20483300)	Sheffield University, 2009 (Appendices)
Female sexual offences slope parameter	0.06583	0.013167[b]	Gamma(25,0.00263)	Sheffield University, 2009 (Appendices)
Female homicide rate	0.00001	0.000001[b]	Beta(134,20483300)	Sheffield University, 2009 (Appendices)
Female homicide slope parameter	0.06583	0.013167[b]	Gamma(25,0.00263)	Sheffield University, 2009 (Appendices)

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Costs				
Cost of causing death by dangerous driving	£1,794,890	358978[b]	Gamma(25,71796)	Sheffield University, 2009 (Appendices)
Cost of more serious wounding	£26,354	5271[b]	Gamma(25,1054)	Sheffield University, 2009 (Appendices)
Cost of less serious wounding	£9,911	1982[b]	Gamma(25,396)	Sheffield University, 2009 (Appendices)
Cost of assault on a constable	£1,772	354[b]	Gamma(25,71)	Sheffield University, 2009 (Appendices)
Cost of assault without injury	£1,772	354[b]	Gamma(25,71)	Sheffield University, 2009 (Appendices)
Cost of criminal damage	£1,065	213[b]	Gamma(25,43)	Sheffield University, 2009 (Appendices)
Cost of theft from a person	£1,038	208[b]	Gamma(25,42)	Sheffield University, 2009 (Appendices)
Cost of robbery	£8,959	1792[b]	Gamma(25,358)	Sheffield University, 2009 (Appendices)
Cost of robbery (business)	£6,151	1230[b]	Gamma(25,246)	Sheffield University, 2009 (Appendices)
Cost of burglary in a dwelling	£4,020	804[b]	Gamma(25,161)	Sheffield University, 2009 (Appendices)
Cost of burglary not in a dwelling	£3,322	664[b]	Gamma(25,133)	Sheffield University, 2009 (Appendices)
Cost of theft of a pedal cycle	£780	156[b]	Gamma(25,31)	Sheffield University, 2009 (Appendices)
Cost of theft from vehicle	£1,056	211[b]	Gamma(25,42)	Sheffield University, 2009 (Appendices)
Cost of aggravated vehicle taking	£5,091	1018[b]	Gamma(25,204)	Sheffield University, 2009 (Appendices)

Parameters	Mean Value	Standard Error	Distribution if Used in PSA	Reference/Section in submission
Cost of theft of vehicle	£5,091	1018[b]	Gamma(25,204)	Sheffield University, 2009 (Appendices)
Cost of other theft	£780	156[b]	Gamma(25,31)	Sheffield University, 2009 (Appendices)
Cost of theft from shops	£123	25[b]	Gamma(25,5)	Sheffield University, 2009 (Appendices)
Cost of violent disorder	£12,803	2561[b]	Gamma(25,512)	Sheffield University, 2009 (Appendices)
Cost of sexual offences	£38,676	7735[b]	Gamma(25,1547)	Sheffield University, 2009 (Appendices)
Cost of homicide	£1,794,890	358978[b]	Gamma(25,71796)	Sheffield University, 2009 (Appendices)

DRL = drinking-risk level; GP = general practitioner; HDD = heavy drinking day; N/A = not applicable; NHS = National Health Service; PSA = probabilistic sensitivity analysis; PI = psychosocial intervention; PSSRU = Personal Social Services Research Unit; RR = relative risk.

[a] Standard error is based on an assumption of standard error being 10% of the mean value.

[b] Standard error is based on an assumption of standard error being 20% of the mean value.

[c] For RR of harmful events parameters that have two or more beta parameters, Cholesky Decompositions were applied to maintain the correlation between the beta parameters in the PSA.

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

As outlined in Section 7.3.2, the model was closely aligned with the clinical trials throughout the first year of the model, during which the transitions were based on the observed changes in drinking level in ESENSE1, ESENSE2, and SENSE. However, some extrapolation of effects was needed beyond the observed 12 months of data from the clinical trial. As described in Section 7.2.4, those patients who had responded to treatment during the first year (being abstinent or having a low DRL) were modeled in a controlled-drinking health state without treatment. Patients who were defined as not having responded to treatment (high- or very high-risk drinking level) and who discontinued nalmefene + PI or PI were modelled to continue with second-line treatment (assisted alcohol withdrawal followed by acamprosate or naltrexone + PI for relapse prevention). Thus, for patients in both the controlled-drinking and the high/very high-risk drinking level, no extrapolation of effect from the clinical trials was incorporated after the 12-month short-term part of the model.

However, the patient cohort in the medium-risk drinking level after 12 months is assumed to respond to treatment, but not sufficiently so as to stop treatment altogether; these patients therefore remain on nalmefene + PI or PI treatment. According to clinical experts in England and Wales consulted by Lundbeck, this is aligned with clinical practice. To allow for this continued treatment, the effect of the treatment was based on extrapolation of the observed treatment effect for the last 6 months in the SENSE 12-month trial. This was judged to be the most appropriate source of data in this context and was assessed as appropriate by the health economic and clinical experts which Lundbeck consulted. Specifically, the average transition probabilities of the medium-risk drinking level for the last 6 months in the SENSE trial was used to model the yearly transition probabilities from the medium-risk drinking level to controlled drinking or high and very high drinking (the resulting probabilities can be found in Table B51).

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Some assumptions related to both data and model structure were included in the model. The assumptions and related justifications are listed below:

Proportion treated in primary care by the General Practitioner.

The proportion of patients treated by GPs versus in a specialised care setting was based on inputs from clinical experts in England and Wales as part of the collaborations described in Section 7.3.5.

Patients relapsing to a new round of treatment after failing or relapsing from secondary treatment

The proportion of patients relapsing to a new round of treatment after failing or relapsing from secondary treatment was based on clinical expert input in England and Wales as part of the collaborations described in Section 7.3.5.

Patients relapsing to high/very high drinking level with same proportions as when entering treatment

This assumption was made as we had no evidence of how patients would progress in their drinking after a relapse. Thus we modelled the relapse as unconditional on what drinking level the patient relapsed from and as equal for both treatment arms. This was seen as a conservative assumption, as it's not seen as favouring the nalmefene treatment arm. This approach was validated by clinical experts as part of the collaborations described in Section 7.3.5.

Length of tunnel state for temporary harmful events

The length patients stayed in, and incurred costs and QALYs of, the harmful events modelled as temporary health states (lower respiratory infections, transport injuries, and injuries other than from transport) was decided in collaboration with public health experts and was seen as adequate for the length that these harmful events would influence the patients.

Absorptive state for severe events

Modelling the serious events as absorptive health states where the patient would stop drinking and would not be at risk for further harmful events or cost increase and and as QALY decrements due to alcohol dependence was based on the uncertainty around the conditional probability of a second or subsequent harmful event occurring given the first and also the uncertainty of how these events would affect the continued drinking. Thus, to be conservative, these were included as absorptive health states.

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's "Guide to the methods of technology appraisal," Section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

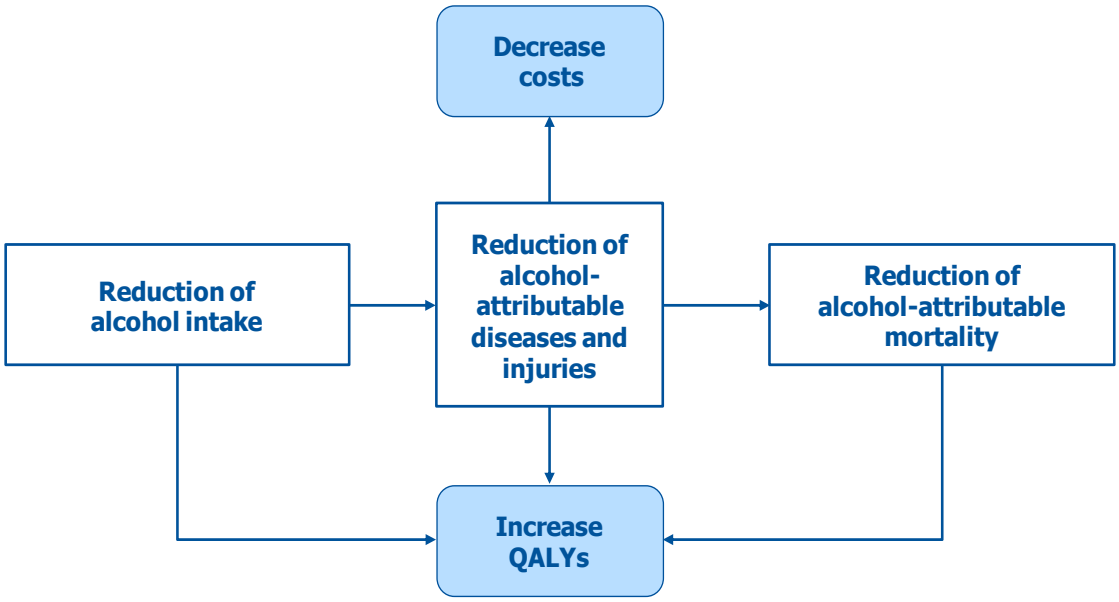
Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

The model examines the ability of compared interventions to reduce alcohol consumption. The reduction of alcohol intake leads to additional QALYs through the reduction of alcohol intake per se, avoidance of alcohol-attributable diseases and injuries, reduced alcohol-attributable mortality, and to cost savings.

Figure B22 illustrates this general concept which was the basis of the nalmefene cost-effectiveness analysis.

Figure B22. Sequence of outcomes in the economic analysis for nalmefene



QALY = quality-adjusted life-year.

The benefits from the alternative interventions are reflected in the impact on patients' HRQL. Reduction of alcohol consumption and the avoidance of alcohol-attributable harmful events (morbidity and mortality) could potentially increase patients' HRQL.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

It has been reported that in general, individuals with substance misuse disorders score significantly lower than population norms on quality of life measures (e.g., SF-36) (Morgan et al., 2003). Additionally, frequent heavy drinking or episodic heavy drinking patterns were associated with reduced quality of life compared to the general population (Donovan et al., 2005). Individuals with alcohol dependence had reported lower levels of quality of life compared with general population norms and other chronic health conditions (Donovan et al., 2005). This is plausible considering that the risk of alcohol-attributable harmful events, for which the development is directly correlated

with the level of alcohol consumption, leads to reduction in patients' quality of life (Sheffield University, 2009; Rehm et al., 2003; Rehm et al., 2009).

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in Section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The EQ-5D and SF-36 questionnaires were used to assess patient's HRQL in ESENSE1, ESENSE2, and SENSE trials (Section 6.3.5).

In line with the NICE reference case, EQ-5D data were used in the base-case analysis of the cost-effectiveness assessment to model the effect of reduction of alcohol consumption with nalmefene. EQ-5D data were derived from the ESENSE1, ESENSE2, and SENSE trials, where data were collected at baseline, week 12 and at week 24. In the SENSE study, EQ-5D data were collected at baseline, week 12, week 24, week 36, and week 52.

The three trials were pooled to estimate utility scores for the cost-effectiveness model. Two sets of utility weights for the drinking health states (from abstinence to very high drinking levels) are incorporated in the model (Table B56).

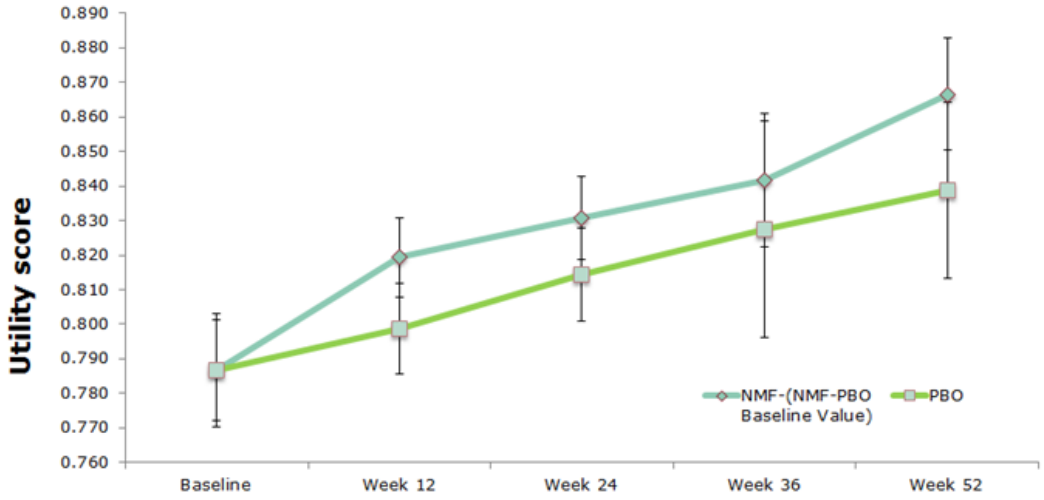
A first set of utility weights was calculated using the area under the curve for the nalmefene and the placebo groups, using pooled EQ-5D data from every point of data collection during the ESENSE1, ESENSE2, and SENSE trials (mean utility score per patient at each time point for compared interventions), thus representing the QALY gain over 1 year for each treatment arm of the nalmefene trials. Specifically, the areas under the curves were calculated with the pooled adjusted mean utility scores for nalmefene and placebo patients from the trials at every 3 months from baseline to 1 year (adjusted on the baseline utility and assuming a linear transition between the mean utilities at each time point). This method of applying utilities from a clinical trial was informed by the NICE Clinical Guideline 100 on alcohol use disorders (NICE, 2010b) and has specific advantage for the accuracy of the model, as the values capture the disutility relating to nalmefene adverse events.

The second set of utility values was derived from the ESENSE1, ESENSE2, and SENSE trials using pooled utility values for "abstinence and low risk" and for "high and very high risk," as there was a negligible difference in utilities between the drinking levels in these groups.

The area-under-the-curve utility weights from the ESENSE1, ESENSE2, and SENSE trial are used in the base-case scenario for the first year of treatment. The area between these curves thus represents the mean effect difference between the two treatment strategies from the first year of treatment; this was considered the most sensitive approach to capture the QALY gain between compared interventions from the nalmefene trials. For years 2 to 5 of the base-case analysis, the pooled utilities from the nalmefene trials were used for high/very high, medium, and low/abstinent groups.

In addition to the utilities from ESENSE1, ESENSE2, and SENSE, an alternate source of utility weights for the effect of reduction of alcohol consumption was tested in a scenario. In this scenario, utility values per drinking level (high/very high, medium, and low/abstinent) from a naturalistic disease management study (STREAM study) of patients with alcohol dependence in the UK primary care setting at the general practitioner level were used (Wallace et al., 2013) (Table B60).

Figure B23. Curves of mean utility scores for nalmefene and placebo over 1 year (ESENSE1, ESENSE2, and SENSE trials)



NMF = nalmefene; PBO = placebo

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Not applicable, as utility values were available measured with the EQ-5D in the clinical trials and utility values for harmful events were identified from sources using the EQ-5D. Thus no mapping was necessary.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in Section 10.12, Appendix 12.

As HRQL data were collected within the clinical trials (ESENSE1, ESENSE2, and SENSE), these utility values were seen to be the most appropriate evidence to use in the cost-effectiveness analysis. Thus, no systematic literature review was performed to identify other sources of HRQL data for the reduction of alcohol consumption.

With regard to HRQL, data used to model the impact of patients experiencing a harmful event on these utility values were derived from the Health Outcomes Data Repository (HODaR) collected in the Cardiff and Vale Hospital Trust in Wales, as reported in the Sheffield Alcohol Policy Model (Sheffield University, 2009). The results from the Sheffield Alcohol Policy Model have also previously been used to underpin recommendations related to alcohol dependence in the NICE Public Health Guidance 24 (NICE, 2010a). The Sheffield Alcohol Policy Model used this data to retrieve utility data from the same source and to limit the potential bias and variability between studies. The data collected in the HoDAR measured utilities in line with the NICE reference case, using EQ-5D valued with the UK tariff (Dolan, 1997), and was based on a large UK (Welsh) population sample of 424,000. The use of these utilities were therefore deemed to the most valid and appropriate for modelling the effect of harmful events on utility. These two attributes—large UK data set and data from same source to avoid potential bias and variability between studies—led to the inclusion of the same dataset for the current model. Thus, no systematic literature reviews were performed for the identification of utility values for the harmful events.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.

- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Utility for alcohol-attributable harmful events

The utilities used for the alcohol-attributable harmful events in the model were, as described in Section 7.4.5, based on the Sheffield Alcohol Policy Model (Sheffield University, 2009), except for the utility score for lower respiratory infections (which was not available in the Sheffield model report).

The utilities used in the Sheffield Alcohol Policy Model were derived from a single source, the HoDAR (2008), to avoid potential bias and variability between studies. The HoDAR data measure utilities using the EQ-5D as recommended by NICE for health economic evaluations. Data used in the Sheffield model were collected by the Cardiff & Vale NHS Hospital Trust serving a local population of 424,000 and providing tertiary care for the whole of Wales. Patients discharged from hospital were requested to complete an EQ-5D questionnaire 6 weeks after their discharge via postal questionnaire. Data were collected on demography, health utility (EQ-5D), and diagnosis (ICD-10). A mean utility value was extracted for each condition based on diagnosis (or ICD-10 codes) and adjusted for age using the percent increment/decrement observed for utilities in the general population (the utility was also assumed to be similar for males and females). The credibility of the utility data published in the Sheffield model is enforced by the fact that this model directly informed recommendations for the NICE public health guidance 24: Alcohol-Use Disorders: Preventing the Development of Hazardous and Harmful Drinking (NICE, 2010a).

The data reported in the Sheffield model and from the HODaR did not include utility scores for respiratory infections. Thus, a targeted review was performed to identify utility values for this health state. This review only identified one publication reporting utilities for respiratory infections resulting in hospitalisation, Sisk and colleagues (2003); therefore, the utility value for respiratory infections was based on this study. However, as the infections and corresponding utility value potentially might be viewed as more severe for the lower respiratory tract infections acquired by the patients in the model described here, an adjustment was made applying the utility for only 9 of the 28 days in the cycle if a respiratory infection was experienced in the model.

It has been suggested in the literature that utility values should be adjusted to account for comorbidities (e.g., using a multiplicative approach) (Ara and Brazier, 2010). This could be seen to be appropriate for the utility values pertaining to the short-term harmful events in the model reported here, as the patients are assumed to continuing to drink despite having the event. Thus, utilities for the harmful events could have been adjusted for drinking level (combining utilities from the drinking level utility and the alcohol-attributable harmful event utility). However, to be conservative in the assumption of the effects on utility, this has not been included in the model.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable, as explained in Section 7.4.6.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Adverse events related to nalmefene were considered only in terms of treatment withdrawal; therefore, no quality of life decrement was specifically applied in the model based on the incidence of adverse events related to nalmefene. However, as the area under the curve from the clinical trials was used for the utility gain during the first year, this also incorporated any reduction in HRQL due to adverse events during the trial period.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in Sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table B56. Utility values, used to calculate the area under the curve

Time	Nalmefene	Standard error	Psychosocial intervention	Standard error	Reference in submission	Justification
Baseline	0.787	0.0146	0.787	0.0164	Section 7.4.3	This method of applying utilities from a clinical trial was informed by the NICE Clinical Guideline 100 on alcohol use disorders (NICE, 2010b) and has the specific advantage in our case to capture both the full treatment effect from the randomised controlled trail as well as the disutility relating to nalmefene adverse events.
Week 12	0.819	0.0115	0.799	0.0132		
Week 24	0.831	0.0121	0.815	0.0135		
Week 36	0.842	0.0193	0.828	0.0313		
Week 52	0.867	0.0163	0.839	0.0256		
Source: ESENSE1, ESENSE2, and SENSE.						

Table B57. Utility values from ESENSE1, ESENSE2, and SENSE, by drinking level used in the base-case analysis

Drinking risk level	Utility	Standard error	Reference in submission	Justification
Very high risk	0.795	0.01	Section 7.4.3	The utility values from the clinical trials (ESENSE1, ESENSE2, and SENSE) were seen to be the appropriate values to use for the base-case analysis, as the resulting values were aligned with the expected effect of the actual patient group being treated and also being aligned with the results for the first-year treatment effect.
High risk				
Medium risk	0.825	0.01		
Low risk	0.862	0.01		
Abstinence				
Source: ESENSE1, ESENSE2, and SENSE.				

Table B58. Utility values for alcohol-attributable serious events

Event	Utility	Standard error	Reference in submission	Justification
Ischaemic heart disease	0.643		Section 7.4.6	These utility values for the harmful events were measured in line with the NICE reference case, using EQ-5D valued with the UK tariff and based on a large UK population sample of 424,000. In addition, due to the use of data from same source, the potential bias and variability between studies were avoided.
Ischaemic stroke	0.564			
Haemorrhagic stroke	0.657			
Cirrhosis of the liver	0.494			
Pancreatitis	0.447			
Source: Sheffield University, 2009.				

Table B59. Utility values for alcohol-attributable short-term events

Event	Utility	Standard error	Reference in submission	Justification
Lower respiratory infections	0.200[a]		Section 7.4.6	These utility values for the short-term harmful events (motor vehicle accidents and injuries other than from transport) were measured in line with the NICE reference case, using EQ-5D valued with the UK tariff and based on a large UK population sample of 424,000. In addition, due to the use of data from same source, the potential bias and variability between studies were avoided. The utility for lower respiratory infections was the only utility value identified in the published literature.
Motor vehicle accidents	0.598			
Injuries other than from transport	0.592			
[a] Utility score for an inpatient acute episode of lower respiratory infection. Source: Sheffield University, 2009; Sisk et al., 2003.				

Table B60. Utility values from STREAM, by drinking level used in a sensitivity scenario

Drinking risk level	Utility	Standard error	Reference in submission	Justification
Very high risk	0.531	0.0450	Section 7.4.3	The inclusion of these utility values from a naturalistic disease management study of patients with alcohol dependence in the UK primary care setting at the general practitioner level was seen to provide a scenario investigating the impact of real-life data from a strictly UK setting.
High risk	0.609	0.0440		
Medium risk	0.714	0.0521		
Low risk	0.755	0.0379		
Abstinence	0.816	0.0549		
Source: Wallace et al., 2013				

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Please see Section 7.3.5 for a description of input from clinical experts for the model.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The basic principle related to the patient experience of HRQL for a patient progressing through the health states in the model is that the patient is experiencing HRQL in line with the drinking level and presence of harmful events. In the short-term section of the model, the HRQL related to the drinking level is accounted for based on the utility value observed during the clinical trials and incorporated in the model based on the area under the curve. During this short-term phase of the model, patients experiencing an harmful event acquire a disutility based on the decrement of utility between the general population and the utility specific to the harmful event.

For the long term of the model, the utilities were fully incorporated based on utility per drinking level and presence of harmful events. Thus, patients were experiencing utility specific to the health state they were in for the time spent in the health state.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects identified in the clinical trials were excluded from the analysis. There are, however, several additional alcohol-attributable harmful events identified in the literature that were not incorporated into the model. 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

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

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 experts based in the UK), which included an assessment of the available evidence in the literature. Importantly, this is seen as a conservative assumption, as incorporation of additional alcohol-attributable harmful events would likely have led to more favourable results for nalmefene due to its ability to reduce alcohol consumption.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable, as no differences in baseline quality of life compared to the health state were assumed.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL was not assumed to be constant over time, with the transitions into different health states affecting HRQL and the resulting utility.

7.4.15 Have the values in Sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable, as no values have been amended.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's "Guide to the methods of technology appraisal," Section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to Section 2.

Not applicable, as we have no evidence of current reference costs for clinical management of the condition.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

We have no evidence that there are more appropriate sources for this analysis, so where possible we have used NHS reference costs as recommended by NICE. All costs are inflated to 2012 costs (PSSRU costs 2011/2012).

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in Section 10.13, Appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

In line with the incorporation of HRQL for the harmful events incorporated in the model, the cost of these events was derived from the Sheffield Alcohol Policy Model (Sheffield University, 2009). As it did with HRQL data, this model incorporated data on costs from large UK studies specifically investigating the cost of the health-related harmful events and crime events incorporated in our model. The Sheffield Alcohol Policy Model used this data to retrieve cost data

from the same source and to limit the potential bias and variability between studies. The data for cost of harmful events in the Sheffield Alcohol Policy Model were taken from work done by the Department of Health (2008) on NHS costs of alcohol-attributable diseases. The costs of crime events were based on unit costs of crime reported by Brand and Price (2000) and Dubourg and colleagues (2005) in studies undertaken on behalf on the Home Office. All costs are inflated to 2012 costs (PSSRU costs 2011/2012).

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Please see Section 7.3.5 for a description of input from clinical experts for the model.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to Sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.

The direct medical costs of treatment consist of the cost of nalmefene + PI in the nalmefene + PI treatment strategy, and the cost of psychosocial intervention alone for the PI treatment strategy (Table B61). For both treatment strategies, in the base-case analysis, the proportion of patients receiving treatment at a GP's practice and the proportion of patients receiving treatment at the specialist level were both set to 75% being treated at a GP's practice and 25% being treated the specialist level (assumption based on the context of the current medical practice of alcohol dependence in England and Wales). The number of medical consultations was applied as prespecified for the nalmefene trials, from randomisation. It is anticipated that psychosocial intervention will be delivered with or without nalmefene during a usual medical

[7] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

consultation (as during the nalmefene clinical trials) at GP and specialist levels. Excluding the treatment of alcohol-attributable harmful diseases and injuries (which are accounted for separately), no other additional monitoring of patients is anticipated to be required in addition to usual medical care in alcohol dependence for the assessed population.

Table B61. Unit costs associated with nalmefene in the economic model (2012)

Items	Nalmefene + PI	Ref. in submission	Psychosocial intervention	Ref. in submission	Reference
Technology cost	£3.03	Section 1.10	—	—	N/A
Cost of visit to GP	£63 (17.2 minutes)		£63 (17.2 minutes)		PSSRU, 2012
Cost of attendance for specialised care (drug and alcohol services)	£94		£94		
Proportion of visits to GP	75%	Section 7.3.5	75%	Section 7.3.5	Clinical experts
Number of visits, first month, for treatment	3		3		As predefined in clinical trials
Visits per month for nalmefene treatment	1		1		As predefined in clinical trials
GP = general practitioner; N/A = not applicable; PSSRU = Personal Social Services Research Unit.					

Cost of the second-line treatment strategy for alcohol dependence

The second-line treatment strategy includes two steps: assisted alcohol withdrawal to reach abstinence followed by relapse prevention, which includes naltrexone or acamprosate and psychosocial treatment. NICE recommends that all patients have assisted alcohol withdrawal prior to treatment with naltrexone or acamprosate (NICE, 2011a). Three approaches are proposed: secondary care outpatient–assisted withdrawal (£606), home-based assisted withdrawal (£596), or secondary care inpatient–assisted withdrawal (£4,145) (NICE, 2011a).

Also, NICE has estimated that among all patients with alcohol dependence in England and Wales, 84% are mildly alcohol dependent (score 15 or less on the SADQ); 14% are moderately alcohol dependent (scoring between 15 and 30 on the SADQ); and 2% are severely alcohol dependent (scoring more than 30 on the SADQ) (NICE, 2011a). Among the moderate and severe alcohol-dependent population, we assumed that the proportion of patients who would be provided with a community-based programme (home-based or outpatient) for alcohol withdrawal is the same as the proportion with moderate alcohol dependence, and the proportion of patients who would be provided with an inpatient programme for alcohol withdrawal was assumed to be the same as the proportion of patients with severe alcohol dependence. The cost of assisted withdrawal was then calculated by using a weighted average of patients who receive outpatient-assisted withdrawal (43.75%; £606), home-based–assisted withdrawal (43.75%; £596), or inpatient-assisted withdrawal (12.5%; £4,145): £1044 (Table B62).

For prevention of relapse after successful alcohol withdrawal, the use of naltrexone or acamprosate + PI is recommended by the NICE Clinical Guideline 115 (NICE, 2011a). NICE estimated the cost of pharmacological intervention (acamprosate or oral naltrexone), along with the additional monitoring needed when these drugs are prescribed, to be £431(NICE, 2011c). The average cost of psychological interventions received by people is taken from the full NICE guidance and is the mean cost of the three main types of therapy recommended: cognitive behavioural therapies, behavioural therapies or social network, and environment-based therapies. The cost for behavioural therapies was estimated by NICE to be £741 (one 60-minute session per week for 12 weeks) (NICE, 2011c). Thus £431 + £741 = £1,172 for relapse prevention treatment (Table B62).

Table B62. Unit costs associated with secondary abstinence treatment (2011)

Item	Cost (£)	Source
Assisted withdrawal	1,044	NICE, 2011c
Outpatient (43.75% of patients)	606	
Home based (43.75% of patients)	596	
Inpatient (12.50% of patients)	4,145	
Relapse prevention programme	1,172	
Acamprosate or oral naltrexone management	431	
Behavioural therapies	741	

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in Section 7.2.4.

Alcohol-attributable harmful events

Alcohol-attributable harmful events have costs attributable to the event code from the International Classification of Diseases, 10th Revision. These costs were derived from the Sheffield Alcohol Policy Model, version 2.0 (Sheffield University, 2009). When an alcohol-attributable harmful event is associated with multiple ICD codes, its costs are calculated using a weighted average based on the admissions reported in Hospital Episode Statistics (2011-2012) for England (data used for modelling the incidence of alcohol-attributable events). The costs in the Sheffield report were adjusted to 2011/2012 costs, using (PSSRU) (Table B63).

The cost for lower respiratory infections was calculated from the NHS reference cost database 2011-2012 (weighted average using Elective Inpatient HRG Data; Currency Code DZ11A, DZ11B, DZ11C, DZ23A, DZ23B, DZ23C).

Table B63. List of alcohol-attributable harmful event costs (2012)

Event	Cost	Reference in submission
Road traffic accident	£5,468	Section 7.2.4
Fall/other injury	£5,296	Section 7.2.4
Ischaemic heart disease	£2,491	Section 7.2.4
Ischaemic stroke	£4,088	Section 7.2.4
Haemorrhagic stroke	£5,799	Section 7.2.4
Cirrhosis of the liver	£3,750	Section 7.2.4
Pancreatitis	£4,373	Section 7.2.4
Lower respiratory infections	£2,999	Section 7.2.4

Societal cost of alcohol consumption

As requested in the scope, the model has included impact of treatment of alcohol dependence on societal costs. The model included societal costs related both to crime issues and productivity. Alcohol is involved in a substantial proportion of crime and up to 50% of violent crime (Australian Institute of Health and Welfare, 2002; Ireland and Thommeny, 1993; Stevenson et al., 1999; Graham and West, 2001), and several studies have reported on the association between excessive drinking and unemployment or absence from work (MacDonald and Shields, 2004; Jarl and Gerdtham, 2012; Roche et al., 2008; French et al., 2011). However, to stay within the NICE reference case, only the societal costs related to crime have been reported here.

To incorporate the crime cost of alcohol consumption in the model, the methods reported by Sheffield University that assessed the effectiveness and cost-effectiveness of public health–related strategies and interventions to reduce alcohol-attributable harm in England (Sheffield University, 2009) has been used. That report looked at the economic consequences of hazardous and harmful drinking and was used to produce the NICE guideline *Alcohol Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence* (NICE, 2011a). Its methods for incorporating the societal costs follow the same methodological concept as used in the current model to model the effect and cost of alcohol-related harmful events (Section 7.3.2) and as show in the equation below.

$$\text{Personal Risk (i)} = \text{Population Risk (i)} \times \text{RR(i)(x)},$$

where *Personal Risk (i)* is the risk of an event *i* for a time period; *RR (i)(x)* is the relative risk of having the event *i* given alcohol consumption of *x*; and *Population Risk (i)* is the risk of event *i* in the general population (including alcohol-attributable and nonalcohol-attributable events). Contrary to the incorporation of the alcohol-related harmful events as described in Section 7.3.2, the incorporation of crime only affects the costs in the model and not health state transitions or QALYs. The specific data used to calculate the crime costs using the approach given above are described in the next sections.

Crime issues

Baseline volume of offences

The types of crime (Table B64) and baseline volume of offences (population risk) used in the model were taken from the Sheffield Alcohol Policy Model (Sheffield University, 2009), which in turn took the volume of offences from a Department of Health (2008) report. The number of offences was incorporated for the population aged 18 years and above and divided by sex (**Error! Reference source not found.** and **Error! Reference source not found.** in Appendix 16).

Risk function parameters

As with the volume of offence, the risk function parameters for crime (relative risks given alcohol consumption) were taken from the Sheffield Alcohol Policy Model (Sheffield University, 2009). The risk function parameter taken from the Sheffield Alcohol Policy Model was the slope parameter. The slope parameters used in the Sheffield model were calculated based on the alcohol-attributed fractions of crimes reported in The Offending Crime and Justice Survey for 2005 (Home Office, 2008). As the alcohol-attributed fractions and resulting slope parameters reported were only given for the ages under 16 years and for ages 16 to 25 years, we incorporated the 16 to 25 slope parameter in line with what was used in the Sheffield Alcohol Policy Model (**Error! Reference source not found.** and **Error! Reference source not found.** in Appendix 16). The alcohol consumption used to model the increased risk of crime was based on the acute drinking levels (HDD) (Table B53 and Table B54) rather than the average drinking level (TAC), as there is no time delay.

Table B64. Crimes included in the model

	Code
Causing death by dangerous driving	4.6
More serious wounding	5
Less serious wounding	8A+D
Assault on a constable	104
Assault without injury	105A+B
Criminal damage	56-59
Theft from a person	39
Robbery	34
Robbery (business)	34A
Burglary in a dwelling	28+29
Burglary not in a dwelling	30+31
Theft of a pedal cycle	41
Theft from vehicle	45
Aggravated vehicle taking	37.2
Theft of vehicle	48
Other theft	49
Theft from shops	46
Violent disorder	65
Sexual offences	N/A
Homicide	1+4+37

Cost of offences

The unit costs of crime used in the model were the ones used in the Sheffield Alcohol Policy Model (Sheffield University, 2009) where they had extracted the unit cost of crime from Brand and Price (2000) and Dubourg and colleagues (2005). These unit costs take into consideration several

dimensions such as cost in anticipation of crime and cost to the justice system (Table B65).

Table B65. Unit cost of crime (2012)

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

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in Section 6.9 (Adverse events). These should include the costs of therapies identified in Sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.

In the nalmefene clinical trial programme (ESENSE1, ESENSE2, and SENSE), the adverse events associated with nalmefene with the highest incidence were nausea, dizziness, insomnia, and headache (Section 6.4.1). It was not expected that these adverse events would be associated with significant additional costs; therefore, the model does not incorporate costs associated with drug adverse events. However, adverse events related to nalmefene are directly linked to withdrawal from treatment in the model.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's "Guide to the methods of technology appraisal," Sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

To investigate the impact of using different assumptions and data, the model was run with different scenarios judged of interest and presented in Table B66. These scenarios are testing the impact on the result of varying the time horizon, assuming nalmefene intake on every day that the patient is in the model, perspective on cost, utility data used, and removing the second-line treatment option.

Table B66. Scenario analyses performed in the economic analysis of nalmefene cost-effectiveness

Analysis	Time horizon	Nalmefene intake	Second-line treatment option	Cost perspective	Utility	Rationale
Base-case analysis	5 years	As needed	Yes	Healthcare	ESENSE1, ESENSE2, and SENSE	This scenario was judged to be conservative and to illustrate appropriately the real-life effectiveness of compared interventions, and this for an appropriate time horizon limiting the uncertainty of the results
Scenario 1	1 year	As needed	Yes	Healthcare	ESENSE1, ESENSE2, and SENSE	Idem as the base-case analysis but using a within-trial time horizon
Scenario 2	5 years	As needed	Yes	Societal perspective	ESENSE1, ESENSE2, and SENSE	Idem as the base-case analysis but investigating the impact on wider societal costs by including cost of crime over 5 years
Scenario 3	1 year	As needed	Yes	Societal perspective	ESENSE1, ESENSE2, and SENSE	Idem as the base-case analysis but investigating the impact on wider societal costs by including cost of crime for 1 year
Scenario 4	5 years	Every day	Yes	Healthcare	ESENSE1, ESENSE2, and SENSE	Idem as the base-case analysis but using higher drug-related costs to account for the highest possible nalmefene intake (worst case in clinical practice)
Scenario 5	5 years	As needed	No	Healthcare	ESENSE1, ESENSE2, and SENSE	This scenario shows the effect of nalmefene + PI versus PI outside the treatment sequence context in England and Wales. For this scenario, patients drinking at high or very high level at 12 months continue to drink at that level up to 5 years.
Scenario 6	5 years	As needed	Yes	Healthcare	STREAM	Idem as the base-case analysis but using utility scores most differentiating the treatment effect in terms of alcohol consumption and alcohol-attributable events
Scenario 7	As the base case but increasing the treatment effect of PI relative to the nalmefene + PI arm to identify a threshold effectiveness for when nalmefene + PI would no longer be cost-effective compared to PI at a willingness-to-pay threshold of £20,000 and £30,000.					This scenario has been included to investigate how an improved treatment effect for PI vs. nalmefene + PI would affect the cost-effectiveness.

Analysis	Time horizon	Nalmefene intake	Second-line treatment option	Cost perspective	Utility	Rationale
Scenario 8	As the base case but without any costs associated with the PI treatment.					This scenario has been included to investigate how a decrease to no costs of PI treatment would affect the cost-effectiveness of nalmefene + PI vs. nalmefene + PI.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in Section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The one-way sensitivity analysis was performed to test the robustness of the model assumptions and specific parameter estimates given their uncertainty. An automated one-way sensitivity analysis, in which one specific parameter is varied at a time while others are held constant, was run for model parameters and was based on a credible range of estimates derived from the data.

The number of parameters tested was 232 (full list in Section 7.3.6). This corresponds to all model parameters except the transition probabilities between drinking levels and dropouts, which were based on the counts from ESENSE1, ESENSE2, and SENSE trials. These were, however, varied in the probabilistic sensitivity analysis as well as in a scenario identifying the threshold effectiveness of PI compared to nalmefene + PI for nalmefene + PI to be cost-effective.

The ranges tested were based on the statistical uncertainty around the estimates when available. The ranges tested for the model parameters that were varied in the one-way sensitivity analysis were based on the 95% CI using the standard error (SE) for the majority of the parameters (see Table B55). However, for some parameters, a range defined as interval of interest (assumption) was tested. Table B67 lists the parameters varied using a range of interest.

Table B67. Parameters varied in the one-way sensitivity analysis using a range of interest

Parameters	Mean Value	Range Tested
Discount rate - cost	0.035	0 to 0.06
Discount rate - outcomes	0.035	0 to 0.06
Proportion of day at risk of road traffic accident (hours)	3	0.5 to 4
Proportion of day at risk of other accidents (hours)	3	0.5 to 4
Proportion of visits to GP (and inversely to specialised care)	75%	0 to 1
Number of visits first month for nalmefene treatment	3.00	1 to 4
Number of visits first month for PI treatment	3.00	1 to 4
Medical visits per month for nalmefene	1.00	0.5 to 2
Medical visits per month for PI treatment	1.00	0.5 to 2
Proportion having again second-line treatment following relapse	0.50	0 to 1
Proportion drinking very high & high having again second-line treatment following relapse	0.50	0 to 1
GP = general practitioner; PI = psychosocial intervention.		

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in Section 7.3.6, including the derivation and value of "priors." If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A probabilistic sensitivity analysis (PSA) was undertaken in which all parameters estimated with uncertainty were varied at the same time and were run for 5,000 iterations. Uncertainty around model parameter estimates is based on their calculated or reported patient counts, standard errors, or range, depending on the parameter (please refer to Section 7.3.6 for the full list of parameters and additional details of the probabilistic sensitivity analysis).

From the 5,000 Monte-Carlo simulations, the 2.5th and 97.5th percentiles were used to present 95% CI for the differences between the compared cohorts for total cost, life-years, and QALYs. Table B68 displays the model inputs and their associated distributions used in the probabilistic sensitivity analysis. The distribution used for each parameter can be found in Section 7.3.6.

Table B68. Inputs and associated distributions used in the probabilistic sensitivity analysis

Input(s)	Distribution	Distribution Description and Bounds
Transition probabilities, utility weights	Beta and Dirichlet	Conjugate prior to the binomial distribution Dirichlet is the multivariate generalisation of the beta distribution Bounded by 0 and 1
Relative risks (alcohol-attributable harmful events)	Log-normal	Confidence intervals for relative risks are calculated on a log scale Therefore, the log-normal distribution is selected Bounded by 0 and positive infinity
Costs	Gamma	Conjugate prior to many distributions, including the normal distribution, Poisson, and exponential Bounded by 0 and positive infinity

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

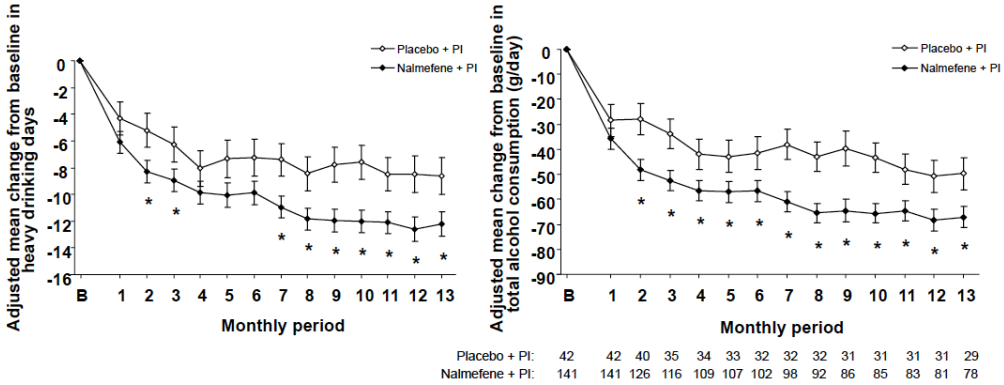
- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see Section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Similar development in reduction of drinking level can be seen when comparing the health state occupation of patients in the model with what was seen in the clinical trials (Figure B24, Figure B25, and Figure B26). However, as the model assumed that patients dropping out from treatment or relapses back to high and very high drinking level more patients are staying within the high very high drinking level in the model compared with the clinical trials. This is the same for both treatment arms in the model.

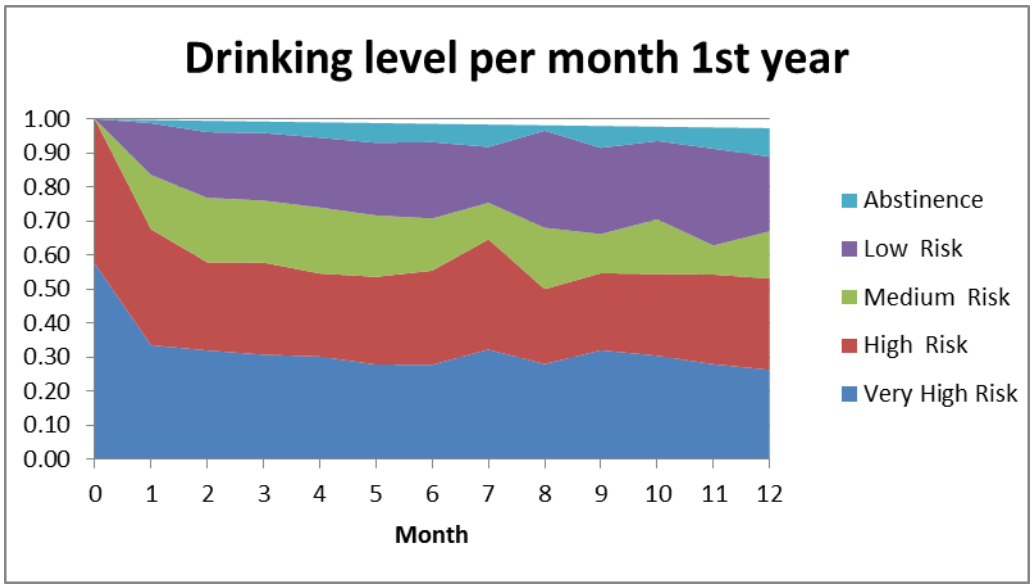
Figure B24. Change from baseline to month 13 in the number of HDDs and TAC observed among patients with a high/very high DRL in SENSE (FAS, MMRM): licensed population



* *P* < 0.05.

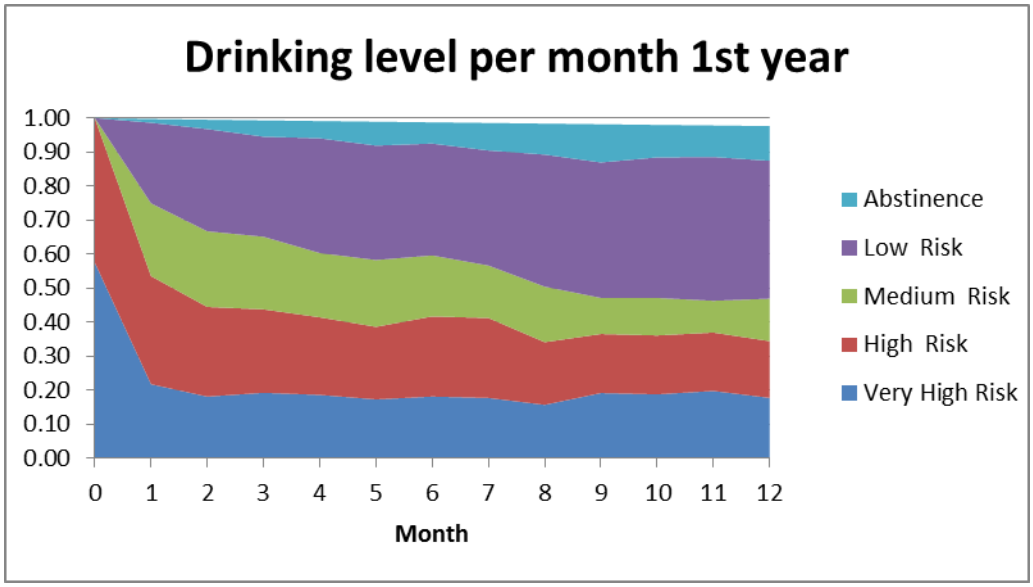
DRL = drinking risk level; FAS = full analysis set; HDD = heavy drinking day; MMRM = mixed model repeated measures; PI = psychosocial intervention; TAC = total alcohol consumption.

Figure B25. Proportion of patients, per WHO DRL, for PI, year 1



DRL = drinking risk level; WHO = World Health Organization.

Figure B26. Proportion of Patients, per WHO DRL, for nalmefene + PI, year 1



DRL = drinking risk level; WHO = World Health Organization.

The use of nalmefene led to a reduction of all harmful events, with regard to both mortality and morbidity, when compared with the psychosocial intervention strategy (Table B69). At 5 years, the use of nalmefene + PI led to the avoidance of 4,857 alcohol-attributable diseases/injuries and 250 deaths per 100,000 patients versus PI.

Table B69. Number of patients experiencing harmful events at year 5 per 100,000 patients

	Nalmefene + PI	PI	Difference (psychosocial − nalmefene)
Harmful events			
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

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

During the first year of the model, the use of nalmefene considerably reduced the number of high-risk and very high-risk drinkers, and increased the number of low-risk drinkers, when compared to treatment with PI. Thus, fewer patients required a second-line abstinence treatment option (Table B70 and Table B71). Ultimately, a greater proportion of patients were in control of their drinking (controlled-drinking health state at 5 years).

Table B70. Proportion of patients per health state in the model – nalmefene + PI

	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.

Table B71. Proportion of patients per health state in the model – PI

	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.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table B72. QALYs accrued over time: nalmefene + PI

	QALY drinking health states	QALY serious harmful events[a]	QALY short-term events[a]	Total QALYs
Year 1	0.803	−0.002	−0.001	0.800
Year 2	1.539	0.014	0.005	1.558
Year 3	2.222	0.040	0.021	2.278
Year 4	2.867	0.075	0.036	2.967
Year 5	3.476	0.118	0.050	3.624

QALY = quality-adjusted life-year.

[a] Negative quality values year 1 for the serious harmful and short-term events are due to the use of disutility's for these health states subtracted from the area under the curve utility from ESENSE 1 & 2 and SENSE (see Section 7.4.11).

Table B73. QALYs accrued over time: nalmefene + PI

	QALY drinking health states	QALY serious harmful events[a]	QALY short-term events[a]	Total QALYs
Year 1	0.787	−0.002	−0.001	0.784
Year 2	1.510	0.015	0.005	1.529
Year 3	2.170	0.043	0.028	2.235
Year 4	2.794	0.081	0.047	2.909
Year 5	3.381	0.128	0.067	3.553

QALY = quality-adjusted life-year.

[a] Negative quality values year 1 for the serious harmful and short-term events are due to the use of disutility's for these health states subtracted from the area under the curve utility from ESENSE 1 & 2 and SENSE (see Section 7.4.11).

7.7.4 Please indicate the life-years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table B74. Model outputs by clinical outcomes: nalmefene + PI

Outcome	Life-year	QALY	Cost (£)
Drinking health states	4.129	3.476	3,625
Serious harmful events	0.192	0.118	183
Short term events	0.092	0.050	637

QALY = quality-adjusted life-year.

Table B75. Model outputs by clinical outcomes: PI

Outcome	Life-year	QALY	Cost (£)
Drinking health states	4.076	3.381	3,811
Serious harmful events	0.210	0.128	204
Short term events	0.119	0.067	828
QALY = quality-adjusted life-year.			

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table B76. Summary of QALY gain by health state

Health state	QALY nalmefene	QALY psychosocial intervention	Increment	Absolute increment	% absolute increment
Drinking health states	3.476	3.381	0.095	0.095	77%
Serious harmful events	0.118	0.128	-0.011	0.011	9%
Short-term events	0.050	0.067	-0.017	0.017	14%
Total	3.624	3.553	0.071	0.122	100%
QALY = quality-adjusted life-year.					

Table B77. Summary of costs by health state (2012)

Health state	Cost nalmefene	Cost psychosocial intervention	Increment	Absolute increment	% absolute increment
Drinking health states	£3,625	£3,811	−£186	£186	47%
Serious harmful events	£183	£204	−£21	£21	5%
Short-term events	£637	£828	−£190	£190	48%
Total	£4,445	£4,842	−£397	£397	100%

Table B78. Summary of predicted resource use by category of cost (2012)

Item	Cost nalmefene	Cost psychosocial intervention	Increment	Absolute increment	% absolute increment
Cost of medical treatment	£1,304	£1,165	£139	£139	7%
Nalmefene cost	£621	£0	£621	£621	32%
Cost of harmful events	£821	£1,032	−£211	£211	11%
Cost of secondary abstinence treatment	£1,699	£2,646	−£947	£947	49%
Total	£4,445	£4,842	−£397	£1,919	100%

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table B79. Base-case results[a]

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (95% CI)	Incremental LYG (95% CI)	Incremental QALYs (95% CI)	ICER incremental (QALYs)
PI (standard care)	£4,842	4.404	3.553				
Nalmefene + PI	£4,445	4.413	3.624	−£397 (−£1,068 to £81)	0.009 (0.005 to 0.018)	0.071 (0.042 to 0.141)	Nalmefene dominates. Probability of cost-effectiveness £20k and £30k is 100%

ICER = incremental cost-effectiveness ratio; LYG = life-years gained; PI = psychosocial intervention; QALYs = quality-adjusted life-years.

[a] Results based on deterministic analysis.

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

The one-way sensitivity analysis for the base-case scenario varied one parameter at a time while others were held constant. 232 parameters were varied in this analysis. The 20 parameters most affecting cost-effectiveness are presented in Table B80. A full list of the parameters varied in the sensitivity analysis and ranges applied are presented in Appendix 16. Of the parameters included in the one-way sensitivity analysis, the ones with most impact on cost-effectiveness are the number of medical visits per month (for both treatments), the proportion of having treatment following relapse, the utility value used, and the cost of nalmefene. Nalmefene + PI remained cost saving when varying all of these parameters, except for medical visits per month; when applying this parameter's upper bound, the ICER increased to £6,274.

Considering the base-case analysis as reference, none of the analyses questioned the cost-effectiveness of nalmefene or the robustness of the base case analysis.

Table B80. Individual parameters most affecting the cost-effectiveness base-case results in the one-way sensitivity analysis

Parameter	ICER at lower bound[a]	ICER at upper bound[a]	Mean value (range tested)
Medical visits per month nalmefene	−£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 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)

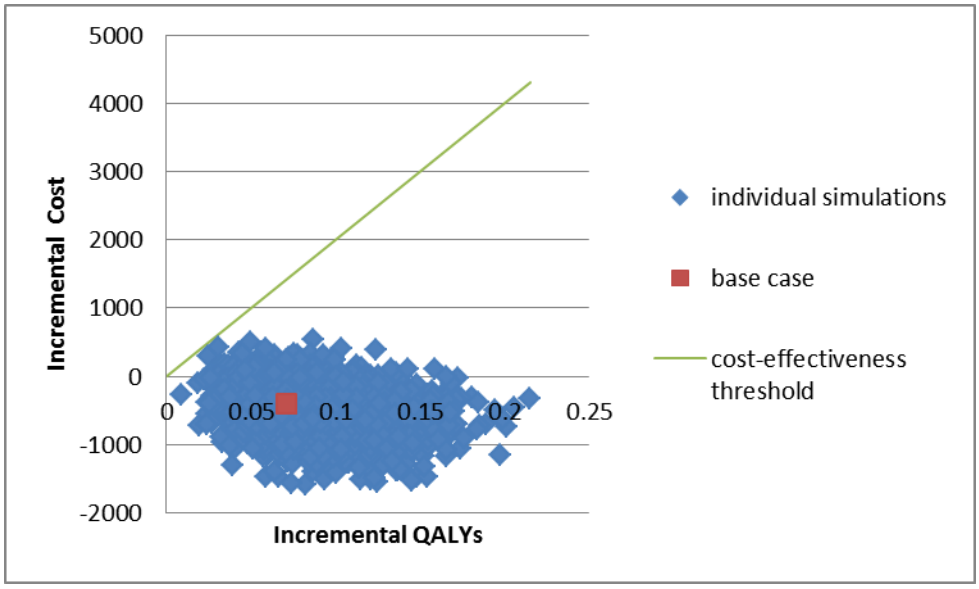
Parameter	ICER at lower bound[a]	ICER at upper bound[a]	Mean value (range tested)
Discount rate: outcomes	−£5,028	−£5,975	3.5 (0-0.06)
Proportion of visits to GP (to specialized care)	−£4,929	−£5,786	0.75 (0-1)
Male RR other injury	−£5,281	−£6,030	2.19 (1.7-2.19)
Male RR mortality due to cirrhosis of 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.

[a] Lower and upper bound refers to the minimum and maximum parameter value tested in the one-way sensitivity analysis (see Section 7.6.2).

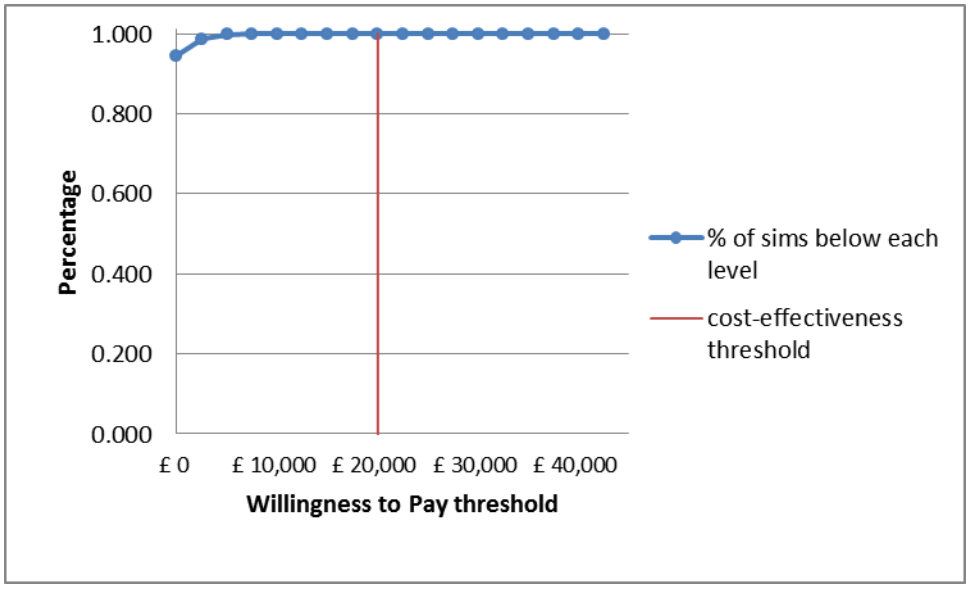
7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure B27. Results of the base-case analysis, cost-effectiveness scatter plot



* Cost-effectiveness threshold of 20,000 per QALY gained.

Figure B28. Results of the base-case analysis, cost-effectiveness acceptability curve



The results of the probabilistic sensitivity analysis show that the uncertainty around all parameters included in the model does not influence the conclusion of the base-case analysis. Therefore, the conclusion of the base-case analysis is robust with regard to the parameter uncertainty.

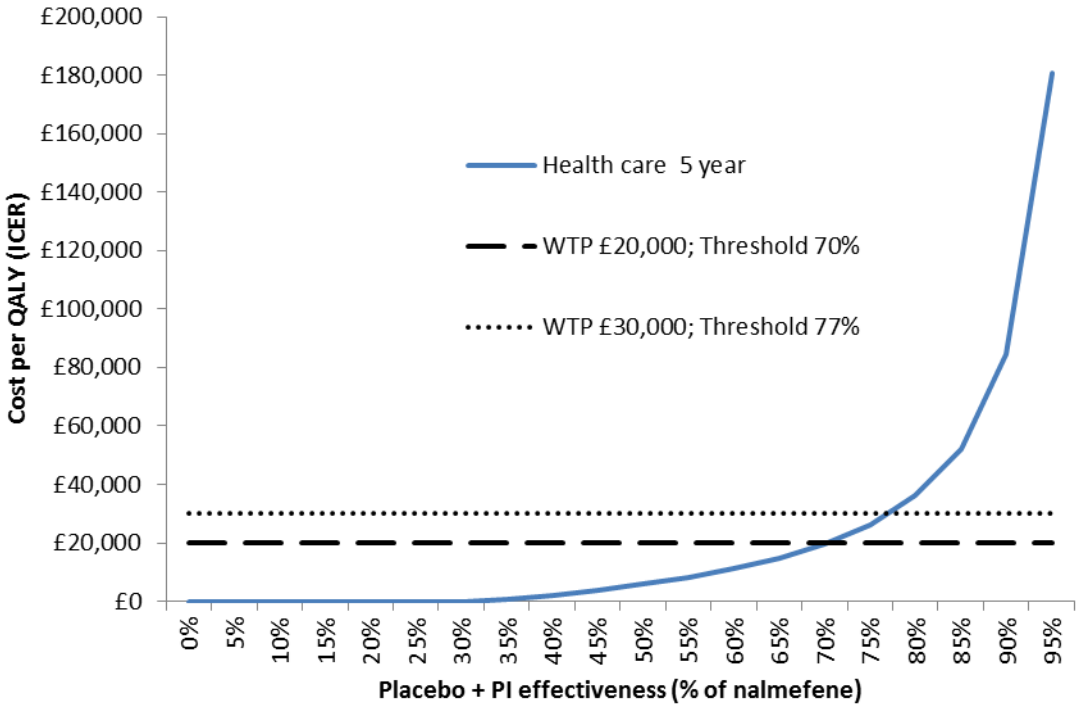
7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table B81. Summary of results of scenario analyses performed in the economic analysis of nalmefene vs. psychosocial support

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/QALY (£)
	NMF + PI	PBO + PI	NMF + PI	PBO + PI	NMF + PI	PBO + PI				
Base-case analysis	£4,445	£4,842	4.413	4.404	3.624	3.553	-£397	0.009	0.071	Nalmefene dominates
Scenario 1	£1,571	£1,162	0.959	0.957	0.800	0.784	£408	0.002	0.017	£24,684
Scenario 2	£15,632	£18,524	4.413	4.404	3.624	3.553	-£2,893	0.009	0.071	Nalmefene dominates
Scenario 3	£4,999	£5,094	0.959	0.957	0.800	0.784	-£95	0.002	0.017	Nalmefene dominates
Scenario 4	£4,863	£4,842	4.413	4.404	3.624	3.553	£21	0.009	0.071	£289
Scenario 5	£2,959	£2,521	4.406	4.394	3.569	3.483	£438	0.012	0.086	£5,090
Scenario 6	£4,445	£4,842	4.413	4.404	3.122	2.929	-£397	0.009	0.192	Nalmefene dominates
Scenario 7	See Figure B29									
Scenario 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; PBO = placebo; QALY = quality-adjusted life-year.

Figure B29. Results from scenario 7: threshold effectiveness of PI



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

7.7.10 What were the main findings of each of the sensitivity analyses?

Table B82. Main findings from the scenario analyses performed in the economic analysis of nalmefene cost-effectiveness

Analysis	Time horizon	Nalmefene intake	Second-line treatment option	Cost perspective	Utility	Main findings
Scenario 1	1 year	As needed	Yes	Healthcare	ESENSE1, ESENSE2, and SENSE	This scenario showed that the time horizon of the analysis has a large effect on the results of the cost-effectiveness. However, it also showed that not only does nalmefene reduce alcohol consumption, reduce alcohol-related harmful events, and improve quality of life, but it reduces the cost due to subsequent treatments needed of alcohol-dependent patients, which leads to savings for the healthcare system.
Scenario 2	5 years	As needed	Yes	Societal perspective	ESENSE1, ESENSE2, and SENSE	Including the alcohol-related risk of crimes, the analysis showed that treatment of alcohol dependence with nalmefene compared to psychosocial intervention not only could save the healthcare system money in the long run but could be economically beneficial for the wider society.
Scenario 3	1 year	As needed	Yes	Societal perspective	ESENSE1, ESENSE2, and SENSE	When including societal costs due to crime, nalmefene becomes cost saving to the wider society already after 1 year. At the same time, it improves the quality of life for the patients.
Scenario 4	5 years	Every day	Yes	Healthcare	ESENSE1, ESENSE2, and SENSE	Increasing the use of nalmefene in an extreme scenario where the patients use nalmefene every day shows that even under this maximum use of nalmefene it would still be cost saving to the healthcare system and improve the quality of life for the patients.
Scenario 5	5 years	As needed	No	Healthcare	ESENSE1, ESENSE2, and SENSE	Isolating treatment of indicated alcohol-dependent patients to only be treated with either nalmefene + PI or PI, not accounting for the effect nalmefene would have on secondary treatment, shows that even in this isolated and very conservative scenario nalmefene would be highly cost effective.

Analysis	Time horizon	Nalmefene intake	Second-line treatment option	Cost perspective	Utility	Main findings
Scenario 6	5 years	As needed	Yes	Healthcare	STREAM	Using utility values from a real-life population and that were not constrained by the usual inclusion and exclusion criteria in the nalmefene phase 3 randomised controlled trials demonstrate the likelihood of better benefit of the use of nalmefene in real life, in terms of improvements in patient-reported quality of life. As the use of these values shows, this is a clear improvement in quality of life gains compared to the results from the clinical trials.
Scenario 7	As the base case but increasing the treatment effect of PI relative to the nalmefene + PI arm to identify a threshold effectiveness for when nalmefene + PI would no longer be cost effective compared to PI at a willingness-to-pay threshold of £20,000 and £30,000.					Running this scenario showed that the treatment with BRENDA alone (PI) would need to have an increased treatment effect of 70% to 77% for nalmefene + PI not to be cost-effective compared to PI. This shows that the results are robust to a substantial change in treatment effect. Given that a comparison with other types of psychosocial interventions (e.g., CBT) was not possible, this scenario analyses also indicates the magnitude of increased effectiveness required of a psychosocial intervention compared to BRENDA + placebo to alter nalmefene's cost-effectiveness. However, it should be noted that BRENDA is among the least intensive forms of psychosocial supports provided and therefore also likely to be less costly than, for example, CBT. Thus, CBT would likely need an even greater effect compared to nalmefene + PI for nalmefene not to be considered cost-effective.
Scenario 8	As the base case but without any costs associated with the PI treatment.					This scenario shows that even when the cost of PI is set to 0 (no treatment visits), but maintaining the treatment effect, treatment with nalmefene would still be cost-effective. Thus, should a cheaper alternative to BRENDA with equal effect become available, nalmefene + PI would still be cost-effective.

CBT = cognitive behavioral therapy; PI = psychosocial intervention.

7.7.11 What are the key drivers of the cost-effectiveness results?

A main driver of the cost-effectiveness results was the proportion of patients within drinking levels as informed by the nalmefene clinical studies.

The effectiveness of nalmefene + PI versus PI in terms of the evolution of drinking was assessed by the model for the first year based on pooled data from the ESENSE1 and ESENSE2 trials and the SENSE trial (see Section 7.2.1), from which the monthly transition probabilities between the five different drinking levels were derived. The monthly transition probabilities were based on the count of patients (observed cases) each month in each WHO health state from the three pooled nalmefene trials. The monthly proportion of patients by drinking levels, to which the risk for alcohol-attributable harmful events was applied, was a main driver of the first year results, but also for the 5-year results, being directly influenced by the relative proportion of patients in different drinking-level categories at 1 year. Thus a main driver of the model is the relative reduction of alcohol consumption between nalmefene + PI versus PI in the three pooled nalmefene trials. As presented in Section 7.2.1 above, pooling the three trials led to relative statistically significant results between compared treatment arms in terms of reduction in monthly TAC and number of HDDs, and also with regard to the responder analysis, which explains the additional benefit resulting from the model from the use of nalmefene + PI versus PI. This assessment of evolution of drinking can also be seen in Table B83, Figure B30, and Figure B31 below.

Parameters for the transition probabilities between drinking levels and dropouts, based on the counts from the ESENSE1 and 2 and SENSE trials (see Appendix 16), were varied in the probabilistic sensitivity analysis. These were incorporated with a Dirichlet distribution based on the counts (and the addition of a uniform prior distribution of 0.01 to correct for zero counts). The probabilistic sensitivity analysis, which considered the uncertainty of parameters in the model with statistical uncertainty (refer to Table B54), including transition probabilities between drinking levels and dropouts, concluded the robustness of the results with regard to parameters uncertainty.

Table B83. Evolution of the proportion of patients per WHO drinking level in the model[a]

	Model entry[b]		Year 1[a]		Year 5	
	Nalmefene + PI	**PI**	**Nalmefene + PI**	**PI**	**Nalmefene + PI**	**PI**
Very high risk	58%	58%	18%	26%	25.1%	39.2%
High risk	42%	42%	17%	27%		
Medium risk	N/A	N/A	12%	14%	4.1%	4.3%
Low risk	N/A	N/A	40%	22%	59.7%	44.3%
Abstinence	N/A	N/A	10%	8%		

DRL = drinking risk level; PI = psychosocial intervention; WHO = World Health Organization.

[a] As described in Section 7.2.1, pooled data from the ESENSE1 and ESENSE2 trials and the SENSE trial have been used to derive the monthly transition probabilities between the five different drinking levels in the model. The monthly transition probabilities were based on the count of patients (observed cases) each month in each WHO health state from the three pooled nalmefene trials.

[b] Patient population in ESENSE1 and 2 and SENSE trials (high and very high WHO DRL at screening and randomisation)

Figure B30. Proportion of patients, per WHO DRL, for PI, Year 1

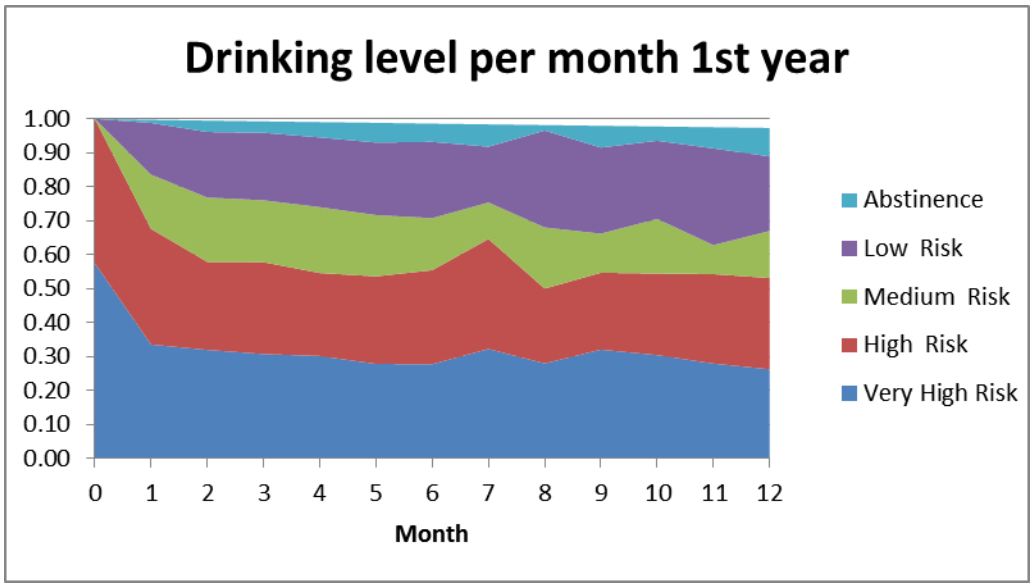
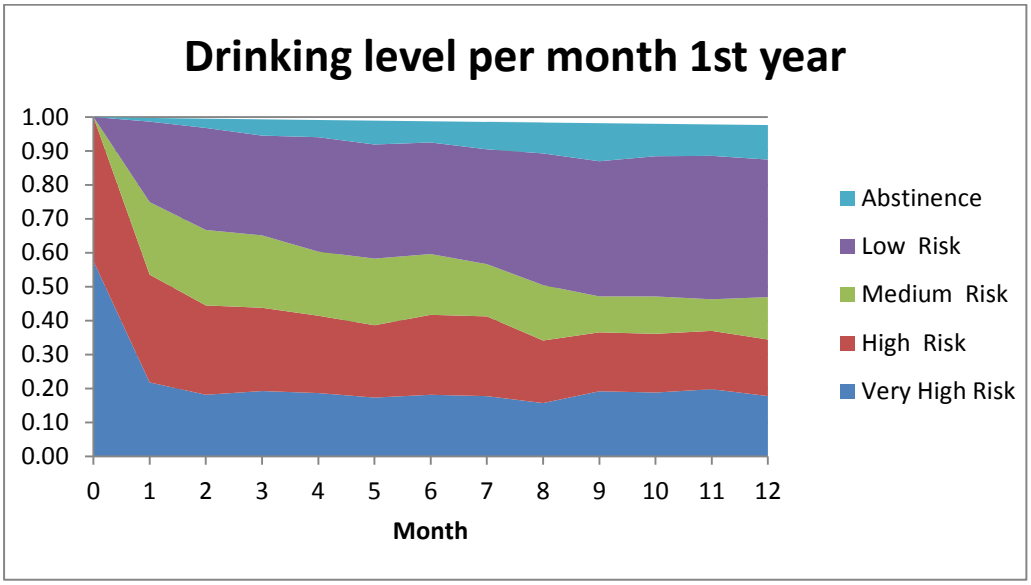


Figure B31. Proportion of Patients, per WHO DRL, for nalmefene + PI, Year 1



Another main driver of the cost-effectiveness results was the utility scores associated with drinking levels. The utilities scores by WHO levels calculated from the nalmefene trial and the QALY gain within trial showed small incremental values. To assess how well the changes in an alcohol-dependent patient's quality of life can be captured, in particular how well can the patient's improvement in terms of level and frequency of drinking become linked with changes in quality of life measures in the context of RCTs, a systematic review of quality of life instruments used as outcome measures in RCTs for alcohol-dependence treatment was performed by Luquiens and colleagues (2012). They reported that available instruments measuring quality of life lack sensitivity to outcome changes in alcohol dependence. Eight instruments in total were identified in this review:

- SF-36
- SF-12
- WHO-QOL-26
- EQ-5D
- APQ
- KoskenvuoQoL Scale
- VASQoL
- TOMHS-HWBS

The most frequently used instrument to measure HRQL in the included studies was a generic health status measure (SF-36). The HRQL instruments identified in this systematic review investigated domains such as relationships with others, activities, physical state, psychological state, financial concerns, medical care, legal problems, and satisfaction with life. Interestingly, these domains were never all covered by one of the instruments identified in the systematic review. In conclusion, the Luquiens study highlighted the heterogeneity of the quality of life instruments used in alcohol-dependent

patients and revealed that the information collected may not be relevant or accurate for this specific patient population.

The quality of life instruments used in the nalmefene trials were the SF-36 and the EQ-5D . The EQ-5D data were used to calculate utilities to incorporate in the current cost-effectiveness analysis as recommended by NICE (2013). The systematic review cited above concluded the lack of sensitivity to outcome changes in alcohol dependence for the EQ-5D instrument. This lack of sensitivity can be interpreted as a lack of correlation between changes in drinking behaviour, level of alcohol consumption, and patient-perceived impact on the dimensions of the generic health status measures, leading to the lack of sensitivity of the EQ-5D to capture the effect of treatment in alcohol dependence and an underestimation of the QALY benefit for nalmefene in this cost-effectiveness analysis.

As shown in sensitivity scenario 6, using utility values from a longitudinal noninterventional study (assessing alcohol-dependent patients in a real-life setting in UK) highly affected the cost-effectiveness. This study assessed a real-life population and was not constrained by the usual inclusion and exclusion criteria in the nalmefene phase 3 RCTs. This is a further demonstration, in addition to the discussion of the Luquiens et al. assessment above, of the likelihood of better benefit of the use of nalmefene in real-life, in terms of improvements in patient-reported quality of life.

Other main drivers were the time horizon (because of the proportion of responders) and the intake of nalmefene. These were varied in the scenario sensitivity analysis, which demonstrated the robustness of the base-case results.

The results of the probabilistic sensitivity analysis show that the uncertainty around all parameters included in the model is not influencing the conclusion of the base-case analysis. In the one-way sensitivity analysis, the parameters with the largest impact on cost-effectiveness were cost saving, except for medical visits per month in the nalmefene arm (ICER of £6,274). However, none of the analyses questioned the cost-effectiveness of nalmefene and the robustness of the base-case analysis. From this, the cost-effectiveness model was stable and showed consistency in various scenarios, confirming the robustness of the model and the cost-effectiveness of nalmefene.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Validation of the model was assured first by the identification of the most appropriate data to be used with regard to the NICE reference case. Additionally, in terms of external validation of the outcome, it involved different components, mainly the external validity in terms of incremental reduction of

drinking for compared treatment arms from the nalmefene clinical trials; and the external validity in terms of number of alcohol-attributable diseases, injuries, and deaths as computed by the model.

The first main external validity aspect was related to the incremental reduction of drinking for the two compared treatment arms of the nalmefene clinical trials. This was assessed with regard to the QALY difference between the two treatment arms. The amplitude of the QALY difference is relatively low. It was assessed and explained by the experts the following way:

- Generic quality of life measures like the EQ-5D are of limited sensitivity in alcohol dependence as concluded by Luquiens and colleagues (2012). There could be insufficient correlation between changes in drinking behaviour and alcohol consumption with patient perceived impact on health status using this measure, which could have led to an underestimation of the QALY gains for nalmefene in this analysis.

- EQ-5D was modelled based on observed case data from the nalmefene clinical trials (without the application of an imputation method for missing data). The use of an imputation method such as the MMRM would have increased the QALY difference.

The second main external validity was related to the number of alcohol-attributable diseases, injuries, and deaths computed by the model. The modelling work on this aspect was performed in close collaboration with the Social and Epidemiological Research Department at the Centre for Addiction and Mental Health in Toronto, Canada, led by Jürgen Rehm. This academic group assessed/evaluated the outcomes from the model and found results to be aligned with their own public health assessments using a similar methodology. This has in the meantime provided additional validation of the comparative effectiveness modeled in terms of comparative reduction of drinking between nalmefene + PI and PI.

In addition to this external validation of the model, quality-control procedures have been performed on the final versions of the cost-effectiveness model and include verification of all input data with original sources, a series of diagnostic tests to confirm that the model is correctly applying all formulas, and review of model calculations and programming.

Quality-control procedures have been performed by reviewers who were not involved in the original development of the model. In addition to general validation of the logic and results of the model, when performing different scenario analyses, the following diagnostic steps have been taken in the quality-control process:

- Verify that all input parameters match original sources.
- Set both treatments to have the same treatment effect and costs.
    - This test demonstrates that the two treatment arms have the same logic and calculations and hence will come to the same results with the same data.

- Check that the number of patients at all stages of the model always sums to the number of patients entering the model.
  - This test ensures that patients are neither entering nor leaving the model—only changing from one state to another.
- Set all costs to 0 and check that the cost of both treatments is 0 for every year.
  - This test demonstrates that all the costs are derived from the values in the “Costs” sheet and that without these (i.e., with them set to £0) the cost of each treatment strategy is £0.
- Exclude harmful events from the model and ensure that the number of deaths is equal between the two treatments.
  - This demonstrates that differences in survival are due to differences in alcohol consumption and not differences in modelling general survival.
- Set all utility values to 1 and check that the number of life-years each year is the same as the number of QALYs.
  - This test demonstrates that all patients alive are being counted in the LYG and QALY calculations.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE’s “Guide to the methods of technology appraisal,” Section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to Section 6.3.7.

As outlined in Section 2.4 and Section 5, it is not relevant to look at subgroups of the licensed population. The reason for this is that the regulatory authorities have already determined the subpopulation of patients with alcohol dependence for whom nalmefene is suitable and has the most benefit (i.e., the nalmefene licence is restricted to a subgroup of patients, namely adults with alcohol dependence who have a high DRL without physical withdrawal symptoms and who do not require immediate detoxification and who continue to have a high DRL 2 weeks after initial assessment). These patients broadly equate to what NICE defines as “mild” alcohol dependence in its clinical guideline. Thus, no subgroup analysis was performed for the cost-effectiveness model.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable; see Section 7.9.1.

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable; see Section 7.9.1.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in Section 7.7.6 (Base-case analysis).

Not applicable; see Section 7.9.1.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in Section 5.

Not applicable; see Section 7.9.1.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Within this pharmacoeconomic analysis, Lundbeck has presented the cost-effectiveness of nalmefene compared to PI in the treatment of patients with alcohol dependence who have a high DRL, without physical withdrawal symptoms, and who do not require immediate detoxification. The results of the base-case analysis demonstrated that treatment with nalmefene resulted in a lower total cost to the NHS in exchange for a higher number of QALYs, compared to PI, which is the mainstay of current clinical practice in this patient population, irrespective of care setting. Therefore, the resulting base-case incremental cost-effectiveness ratio for nalmefene + PI compared to PI at 5 years was dominating for nalmefene, with a 100% probability of cost-effectiveness at a willingness to pay threshold of £20 000 per QALY gained.

Furthermore, the results of the one-way and probabilistic sensitivity analyses support this finding of cost-effectiveness. These analyses included the recording of results when single data inputs in the base case were replaced by their upper or lower confidence intervals (one-way sensitivity analysis) and a comprehensive multiway analysis, where results were recorded using alternative sources of data input to estimate costs and QALYs. The comprehensive sensitivity analyses conducted show that the conclusions are robust to alternative assumptions about model inputs.

In conclusion, the results of the analysis demonstrate that use of nalmefene in accordance with its licensed indication is a cost-effective allocation of healthcare resources in the NHS in England and Wales and may, in certain scenarios, be cost-saving.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in Section 5?

The economic evaluation was performed on the group of patients who continued to have a high/very high DRL despite initial counselling (high/very high DRL at baseline and randomisation in the clinical trial). This is in accordance with the nalmefene product label. Thus, the economic evaluation was performed on the most relevant group of patients for nalmefene.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The objective of this economic analysis is to assess, from the perspective of England and Wales, the cost-effectiveness of nalmefene + PI versus PI for the

treatment of adult patients with alcohol dependence who have a high DRL, without physical withdrawal symptoms, who do not require immediate detoxification, and who continue to have a high DRL 2 weeks after initial assessment. The model can be used to estimate the clinical and economic outcomes resulting from the use of nalmefene + PI, compared with PI. The assessment of nalmefene use in this model was developed as appropriate within the treatment pathways of the medical practice in England and Wales considering alternative treatment options in case of treatment failure.

A clear strength of this model is that it closely follows the data from the clinical trials on nalmefene utilising the transition probabilities between drinking levels directly in the model. This keeps the model close to the actual evidence and keeps assumptions about transitions in the model to a minimum.

The analysis demonstrated the clinical benefit of reduction of alcohol consumption in the assessed population of alcohol-dependent patients. This was demonstrated by the avoidance of alcohol-attributable harmful events (morbidity and mortality) for nalmefene + PI versus PI. The number of events avoided reported from this cost-effectiveness Markov model is likely an underestimation of the number of events to be avoided in real life, mostly because the model used hospital admission data that took into account only the first diagnosis for hospitalisation (alcohol-dependent patients often have multiple alcohol-attributable conditions diagnosed and managed during the same hospitalisation). It was also assumed that patients can have only one serious event at a time, ignoring the non-negligible possibility of comorbidities. In addition, it was also assumed when modelling the short-term events that patients were not having additional risks for these events compared with the general population during days not experiencing an HDD. Finally mortality data were only considered for deaths occurring within 90 days of hospital admission.

Several other conservative assumptions were used in the model, which are described below:

- For serious alcohol-attributable harmful events, a cost was only applied when the event occurred and the patient was removed from the drinking part of the model. However, in real life, ongoing costs are incurred for these events, and a patient experiencing one of these events has an increased risk of another harmful event and thus additional lost QALYs and continued costs.

- The patients dropping out from the trial for reasons other than nalmefene-related adverse events go back immediately to their original drinking level. Furthermore, patients relapsing to treatment after having responded relapse to the same initial treatment effects using the transitions from the baseline populations, even if they have previously shown response to treatment.

- Finally, we modelled a limited number of alcohol-related events for which the published literature showed the strongest evidence-based association between alcohol consumption and these events. Many other alcohol-

attributable events are associated with alcohol dependence, for example, psychiatric comorbidities and cancers that greatly impact patients' quality of life and incur high costs for the healthcare system. We have not incorporated cancers in the model, because it would have required extending the time horizon and thus the uncertainty around the cost-effectiveness results.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Lundbeck believes that the current model has been undertaken using several conservative assumptions or choices related to data used in the model and the structure of the model itself. It is also believed that the scenarios that have been run show that the model results are very robust to various assumptions related to both model structure and data.

However, model was limited by the fact that we considered only direct medical costs of treatment and not the wider impact of alcohol dependence on the population. In addition, we modelled only a limited number of alcohol-attributable harmful events due to limitations in available evidence and the restricted model time horizon. Therefore, it is possible that further relevant costs to the healthcare system or the patient's quality of life from alcohol-attributable harmful events were not included in the model calculations. Furthermore, we did not consider ongoing costs beyond the actual occurrence of an alcohol-attributable harmful event in the model. Finally, when patients withdrew from or failed treatment, we assumed that they would drink continuously at a high or very high DRL for the remaining model time horizon, instead of providing the opportunity for these patients to enter another treatment option. However, this assumption is likely to have underestimated the cost-effectiveness of nalmefene, considering the higher proportion of patients that responded to treatment for nalmefene + PI compared to the proportion of patients that responded to PI.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Epidemiology of alcohol dependence

The European Medicines Agency (EMA) approved nalmefene use within a defined population. A population fitting this definition is the focus of the budget-impact analysis.

To derive the number of these patients eligible to be treated with nalmefene, a top-down approach was used in that the total population in England served as a starting point to estimate the alcohol-dependent population. The full data set used to derive the number of patients that may benefit from nalmefene and the resulting calculations of the patient population are presented in the sections below.

To estimate the alcohol-dependent population, mid-year population estimates (ONS, 2011) for adults were used. Due to the 5-year age bands, the number of adults (aged 18+ years) was calculated by assuming the number of individuals in the age band 15 to 19 was equally spread across the 5 years. The proportion of the number of adults in England with alcohol dependence is based on an assumed prevalence of 5.9% (Fuller et al., 2009). To adjust the patient population with regard to patients dying, numbers of alcohol-related deaths were collected from the ONS Statistical Bulletin (2013).

Proportion of patient cohort with the condition treatable under the licence

Nalmefene is only indicated for a subpopulation of those with alcohol dependence, those without physical withdrawal symptoms, who do not require immediate detoxification, and who continue to have a high or a very high DRL 2 weeks after initial assessment. Patients without physical withdrawal symptoms and who do not require immediate detoxification can, however, be seen to be similar to patients with mild alcohol dependence. Thus, an assumption was made that those patients with mild alcohol dependence were equivalent to the subpopulation of those with alcohol dependence for which

nalmefene is indicated. NICE reported that 84% of patients have mild alcohol dependence, and thus this estimate was used (NICE, 2011a).

The 1-year SENSE study was used as the basis for calculating the proportion of patients with mild alcohol dependence who would be eligible for treatment with nalmefene in accordance with the licence. As described in Section 1.4 (Figure A1), 52% of the patients in the SENSE study drinking at high or very high DRL at baseline had continued to drink at this level at randomisation. In the nalmefene group, 145 patients had a high or very high DRL at screening and randomisation, (i.e., 56% of those with high or very high DRL at baseline).

Thus, the proportion of patients eligible for treatment with nalmefene is assumed to be 84% x 52% x 56% (approximately 24%) of the total population with alcohol dependence (see Table B84).

Estimated proportion of eligible patients with diagnosed alcohol dependence treated with new medicine

To further identify eligible patients that would seek treatment and thus could be treated with nalmefene, the current proportion of patients seeking treatment was used. Alcohol Concern has reported that 6% of those with alcohol dependence in England are currently accessing treatment, and this figure was used for the first-year estimate of patients accessing treatment. However, the introduction of nalmefene can be assumed to lead to a larger proportion of the population accessing treatment. To account for this increase, an annual increase of patients accessing treatment of 4% has been assumed in the model. However, not all patients eligible for nalmefene will receive nalmefene, as this depends on the market shares for nalmefene. Lundbeck has forecasted that nalmefene will reach a market share of 20% in year 1 and a subsequent increase in market share of 10% per year.

Discontinuation rate due to lack of efficacy and adverse events

In the clinical trials, it was shown that 17.5% of the patients would discontinue treatment due to lack of efficacy or adverse events; thus, a reduction of patients staying on treatment aligned with this percentage was included in the model. The resulting patient numbers and percentages can be seen in Table B84.

Table B84. Patient numbers and percentages for England

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated number of patients with the condition	2,425,734	2,446,485	2,467,413	2,488,520	2,509,808
Mortality rate of patient cohort with the condition	6,775	6,775	6,775	6,775	6,775
Net number of patients with the condition	2,418,959	2,439,710	2,460,638	2,481,745	2,503,033
Proportion of patient cohort with the condition treatable under the licence (eligible patients)	24.1%	24.1%	24.1%	24.1%	24.1%
Potential number of eligible patients treatable each year in licence	583,732	588,739	593,789	598,883	604,020
Subpopulation of eligible patient cohort (%)	100%	100%	100%	100%	100%
Estimated proportion of eligible patients treated with new medicine	1.2%	3.0%	5.6%	9.0%	13.2%
Potential number of eligible patients treated each year	7,005	17,662	33,252	53,899	79,731
Discontinuation rate due to lack of efficacy and adverse events	17.5%	17.5%	17.5%	17.5%	17.5%
Number of patients treated in each year	5,779	14,571	27,433	44,467	65,778

Estimates for Wales

Nalmefene has already been approved for use in NHS Wales by the AWMSG. In its submission to the AWMSG, the manufacturer calculated the eligible patient population based on ONS 2011 population estimates for Wales. This gave rise to a total figure of 2,366,063 adults in Wales. Applying the same prevalence rate of 5.9% as for England (APMS, Fuller et al., 2009) gave a total estimate of 139,598 adults in Wales who are alcohol-dependent. Applying the same assumption as for England, that 24.1% of the patient cohort with the condition would be treatable with nalmefene in accordance with the licence**,** the total eligible number of patients in Wales only would be as follows:

- Year 1 2,015
- Year 2 2,700
- Year 3 3,392
- Year 4 4,091
- Year 5 4,798

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

No change was assumed, either in terms of the current clinical pathway or in uptake.

The summary of product characteristics indicates that nalmefene is required to be prescribed in conjunction with continuous psychosocial support. In a primary care/tier 2 service setting, continuous psychosocial support should be considered part of a standard clinical interaction and not a significant change from what would be delivered already in primary care during the routine management of other long-term or chronic conditions. Psychosocial support is routinely offered in tier 2 and tier 3 services.

It was assumed that the introduction of nalmefene would not change the current clinical pathway described in NICE CG115, but would allow for mild alcohol dependence to be successfully managed in a primary care/tier 2 setting more appropriate to the needs of this patient population, as well as a tier 3 setting.

8.3 What assumption(s) were made about market share (when relevant)?

Nalmefene is expected to reach a market share of 20% in the first full year following a positive recommendation from NICE and a subsequent increase in market share of 10% per year.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Not applicable.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

For the reasons given in Section 8.2, only drug acquisition costs were considered in the budget-impact analysis.

8.6 Were there any estimates of resource savings? If so, what were they?

No resource use estimates were included, as the budget-impact analysis only considered drug costs.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

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 MMRM analysis, patients took medication on an average of 56% of days (204 days). The annual budget impact for both of these analyses is detailed in Table B85.

Table B85. Annual budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
England					
OC analysis	£2,223,817	£5,607,067	£10,556,493	£17,111,346	£25,312,032
MMRM analysis	£3,572,115	£9,006,627	£16,956,886	£27,485,942	£40,658,697
Wales					
OC analysis	£127,757	£257,053	£430,602	£649,559	£913,924
MMRM analysis	£205,216	£412,904	£691,676	£1,043,387	£1,468,035
England + Wales					
OC analysis	£2,351,574	£5,864,120	£10,987,095	£17,760,905	£26,225,956
MMRM analysis	£3,777,331	£9,419,531	£17,648,562	£28,529,329	£42,126,732
OC = observed cases; MMRM = mixed model repeated measures.					

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

As shown in the cost-effectiveness analysis, reducing alcohol consumption has been shown to impact societal costs of crime. These savings have not been considered in the budget-impact model.

9 References

Acamprosate (Campral) [summary of product characteristics]. Lyon, France: Merck Santé s.a.s; 2011. Available at: http://www.medicines.org.uk/EMC/medicine/1042/SPC/Campral+EC. Accessed 22 January 2014.

Adamson SJ, Heather N, Morton V, Raistrick D. Initial preference for drinking goal in the treatment of alcohol problems: II. Treatment outcomes. Alcohol Alcohol. 2010;45(2):136-42.

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 22 January 2014.

Alcohol Concern. Key statistics and facts. Available at: http://ac.demo.me.uk/consultancy-and-training/resources2/resources/key-stats-and-facts. Accessed July 2012.

Alden LE. Behavioral self-management controlled-drinking strategies in a context of secondary prevention. J Consult Clin Psychol. 1988 Apr;56(2):280-6.

Alessi SM, Hanson T, Wieners M, Petry NM. Low-cost contingency management in community clinics: delivering incentives partially in group therapy. Exp Clin Psychopharmacol. 2007 Jun;15(3):293-300.

American Psychiatric Association (APA). Fact sheet: substance-related and addictive disorders. 2013. Available at: http://www.dsm5.org/Documents/Substance%20Use%20Disorder%20Fact%20Sheet.pdf. Accessed 22 January 2014.

Anderson P, Baumberg B. Alcohol in Europe: a public health perspective. European Commission; 2006. Available at: http://ec.europa.eu/health/archive/ph_determinants/life_style/alcohol/documents/alcohol_europe_en.pdf. Accessed 21 January 2014.

Anton RF, Pettinati H, Zweben A, Kranzler HR, Johnson B, et al. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol. 2004;24(4):421-8.

Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18. doi:10.1111/j.1524-4733.2010.00700.x.

Australian Institute of Health and Welfare. 2001 national drug strategy household survey: detailed findings. Canberra: Australian Institute of Health and Welfare; 2002.

Barbosa C, Taylor B, Godfrey C, Rehm J, Parrott S, et al. Modelling lifetime QALYs and healthcare costs from different drinking patterns over time: a Markov model. Int J Methods Psychiatr Res. 2010;19(2):97-109.

Barendregt JJ. The half-cycle correction: banish rather than explain it. Med Decis Making. 2009;29(4):500-2

Bierut LJ. Genetic vulnerability and susceptibility to substance dependence. Neuron. 2011;69(4):618-27.

Brand S, Price R. The economic and social costs of crime. United Kingdom: Home Office; 2000.

Brown RL, Saunders LA, Bobula JA, Mundt MP, Koch PE. Randomized-controlled trial of a telephone and mail intervention for alcohol use disorders: three-month drinking outcomes. Alcohol Clin Exp Res. 2007;31(8):1372-9.

Burtscheidt W, Wölwer W, Schwarz R, Strauss W, Gaebel W. Out-patient behaviour therapy in alcoholism: treatment outcome after 2 years. Acta Psychiatr Scand. 2002 Sep;106(3):227-32.

Cobain K, Owens L, Kolamunnage-Dona R, Fitzgerlad R, Gilmore I, Pirmohamed M. Brief interventions in dependent drinkers: a comparative prospective analysis in two hospitals. Alcohol Alcohol. 2011;46(4):434-40.

COMBINE study. Combined pharmacotherapies and behavioural interventions for alcohol dependence: a randomized controlled trial. JAMA. 2006;295(17):2003-17.

Connors GJ, Walitzer KS. Reducing alcohol consumption among heavily drinking women: evaluating the contributions of life-skills training and booster sessions. J Consult Clin Psychol. 2001 Jun;69(3):447-56.

Davidson D, Gulliver SB, Longabaugh R, Wirtz PW, Swift R. Building better cognitive-behavioral therapy: is broad-spectrum treatment more effective than motivational-enhancement therapy for alcohol-dependent patients treated with naltrexone? J Stud Alcohol Drugs. 2007 Mar;68(2):238-47.

Department of Health. Safe, sensible, social - consultation on further action. Impact assessments. 2008.

Disulfiram (Antabuse) [summary of product characteristics]. Hafnarfjordur, Iceland: Actavis Group PTC ehf; 2011. Available at: http://www.medicines.org.uk/EMC/medicine/519/SPC/Antabuse+Tablets++200mg/. Accessed 22 January 2014.

Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35:1095-108.

Donovan D, Mattson ME, Cisler RA, Longabaugh R, Zweben A. Quality of life as an outcome measure in alcoholism treatment research. J Stud Alcohol Suppl. 2005;(15):119-39.

Drummond C, Deluca P, Oyefeso A, Rome A, Scrafton S, et al. Scottish Alcohol Needs Assessment. 2009. Available at: http://www.rcpsych.ac.uk/pdf/SANA%20report%206-8-09%20(2).pdf. Accessed 22 January 2014.

Drummond C, Oyefeso A, Phillips T, Cheeta S, Deluca P, et al. Alcohol needs assessment research project (ANARP). 2005. Available at: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4122239.pdf. Accessed 22 January 2014.

Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996;313(7052):275-83.

Dubourg R, Hamed J, Thorns J. The economic and social costs of crime against individuals and households 2003/04. United Kingdom: Home Office; 2005.

Easton CJ, Mandel DL, Hunkele KA, Nich C, Rounsaville BJ, Carroll KM. A cognitive behavioral therapy for alcohol-dependent domestic violence offenders: an integrated substance abuse-domestic violence treatment approach (SADV). Am J Addict. 2007 Jan-Feb;16(1):24-31.

Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Med Decis Making. 2012;32(5):733-43

English DR, Holman CDJ, Milne E, Winter MG, Hulse GK, Codde JP, et al. The quantification of drug caused morbidity and mortality in Australia. Canberra, Australia: Commonwealth Department of Human Services and Health; 1995. Cited in 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 22 January 2014.

Epstein EE, Drapkin ML, Yusko DA, Cook SM, McCrady BS, et al. Is alcohol assessment therapeutic? Pretreatment change in drinking among alcohol-dependent women. J Stud Alcohol. 2005;66(3):369-78.

Eriksen L. The effect of waiting for inpatient alcoholism treatment after detoxification. An experimental comparison between inpatient treatment and advice only. Addict Behav. 1986;11(4):389-97.

European Association for the Study of the Liver. Clinical practical guidelines: management of alcoholic liver disease. J Hepatol. 2012;57:399-420.

European Medicines Agency (EMA). Guideline on the development of medicinal products for the treatment of alcohol dependence. 2010. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf. Accessed 22 January 2014.

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 22 January 2014.

European Medicines Agency. 2014. Selincro (nalmefene). Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002583/human_med_001620.jsp&mid=WC0b01ac058001d124. Accessed 17 February 2014.

Field CA, Caetano R. The effectiveness of brief intervention among injured patients with alcohol dependence: who benefits from brief interventions? Drug Alcohol Depend. 2010:111(1-2);13-20

Flatley J, Kershaw C, Smith K, Chaplin R, Moon D. Crime in England and Wales 2009/10. Great Britain Home Office; 2010. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/116347/hosb1210.pdf. Accessed 21 January 2014.

François C, Rahhali N, Chalem Y, Torup L, Sorensen P, et al. Consequences of the reduction of alcohol consumption on patient's reported outcomes with the use of nalmefene. 18th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research; 2013. New Orleans, LA.

French MT, Maclean JC, Sindelar JL, Fang H. The morning after: alcohol misuse and employment problems. Appl Econ. 2011:43(21):2705-20.

Fuller E, Jotangia D, Farrell M. Alcohol misuse and dependence. Adult psychiatric morbidity in England, 2007. Results of a household survey. 2009.

Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160(4):636-45.

Graham K, West P. Alcohol and crime: examining the link. In: Heather N, Peters T, Stockwell T, editors. International handbook of alcohol dependence and problems. London: Wiley; 2001. p. 439-70.

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):1432-42.

Gunther OH, Roick C, Angermeyer MC, Konig HH. Responsiveness of EQ-5D utility indices in alcohol-dependent patients. Drug Alcohol Depend. 2008;92(1-3):291-5

Guy W. Assessment manual for psychopharmacology - revised. Rockville, MD: US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration;1976. p. 218-22.

Health and Social Care Information Centre. Hospital Episode Statistics for England. Inpatient statistics, 2011-12; 2012. Available at: http://www.hscic.gov.uk/catalogue/PUB08288. Accessed 19 February 2014.

Heather N, Adamson SJ, Raistrick D, Slegg GP. Initial preference for drinking goal in the treatment of alcohol problems: I. Baseline differences between abstinence and non-abstinence groups. Alcohol Alcohol. 2010;45(2):128-35.

Heather N, Brodie J, Wale S, Wilkinson G, Luce A, Webb E, McCarthy S. A randomized controlled trial of Moderation-Oriented Cue Exposure. J Stud Alcohol. 2000 Jul;61(4):561-70.

Heilig M, Goldman D, Berrettini W, O'Brien CP. Pharmacogenetic approaches to the treatment of alcohol addiction. Nat Rev Neurosci. 2011;12(11):670-84.

Heinälä P, Alho H, Kiianmaa K, Lönnqvist J, Kuoppasalmi K, Sinclair JD. 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):287-92.

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

Hester RK, Squires DD, Delaney HD. 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 Mar;28(2):159-69.

Home Office. Research, development and statistics directorate. Offending Surveys and Research, National Centre for Social Research and BMRB. Social Research, Offending, Crime and Justice Survey; 2005. 2008

Institute of Alcohol Studies (IAS). Alcohol and accidents. 2009.

Ireland CS, Thommeny JL. The crime cocktail: licensed premises, alcohol and street offences. Drug Alcohol Rev.1993;12:143-50.

Jarl J, Gerdtham UG. Does drinking affect long-term sickness absence? A sample selection approach correcting for employment and accounting for drinking history. Appl Econ. 2012;44(22);2811-25.

Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet. 2003;361:1677-85.

Johnson BA, it-Daoud N, Akhtar FZ, Ma JZ. Oral topiramate reduces the consequences of drinking and improves the quality of life of alcohol-dependent individuals: a randomized controlled trial. Arch Gen Psychiatry. 2004;61(9):905-12.

Jung JG, Kim JS, Kim GJ, Oh MK, Kim SS. Brief insight-enhancement intervention among patients with alcohol dependence. J Korean Med Sci. 2011;26:11-6.

Kaempf G, O'Donnell C, Oslin DW. The BRENDA model: a psychosocial addiction model to identify and treat alcohol disorders in elders. Geriatr Nurs. 1999;20(6):302-04.

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):1179-87.

Kavanagh DJ, Sitharthan G, Young RM, Sitharthan T, Saunders JB, Shockley N, Giannopoulos V. Addition of cue exposure to cognitive-behaviour therapy for alcohol misuse: a randomized trial with dysphoric drinkers. Addiction. 2006 Aug;101(8):1106-16.

Keating GM. Nalmefene: a review of its use in the treatment of alcohol dependence. CNS Drugs. 2013;27(9):761-72.

Kranzler HR, 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.

Kranzler HR, Tennen H, Armeli S, Chan G, Covault J, Arias A, et al. Targeted naltrexone for problem drinkers. J Clin Psychopharmacol. 2009;29(4):350-7.

Lahmek P, Berlin I, Michel L, Berghout C, Meunier N, et al. Determinants of improvement in quality of life of alcohol-dependent patients during an inpatient withdrawal programme. Int J Med Sci. 2009;6(4):160-7.

Lam WK, Fals-Stewart W, Kelley ML. Parent training with behavioral couples therapy for fathers' alcohol abuse: effects on substance use, parental relationship, parenting, and CPS involvement. Child Maltreat. 2009 Aug;14(3):243-54.

Leigh G, Hodgins DC, Milne R, Gerrish R. Volunteer assistance in the treatment of chronic alcoholism. Am J Drug Alcohol Abuse. 1999 Aug;25(3):543-59.

Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry. 2012;200(2):97-106.

Litt MD, Kadden RM, Cooney NL, Kabela E. Coping skills and treatment outcomes in cognitive-behavioral and interactional group therapy for alcoholism. J Consult Clin Psychol. 2003 Feb;71(1):118-28.

Litt MD, Kadden RM, Kabela-Cormier E, Petry N. Changing network support for drinking: initial findings from the network support project. J Consult Clin Psychol. 2007 Aug;75(4):542-55.

Litt MD, Kadden RM, Kabela-Cormier E, Petry NM. Changing network support for drinking: network support project 2-year follow-up. J Consult Clin Psychol. 2009 Apr;77(2):229-42.

Litten RZ, Fertig JB, Falk DE, Ryan ML, Mattson ME, et al. A double-blind, placebo-controlled trial to assess the efficacy of quetiapine fumarate XR in very heavy-drinking alcohol-dependent patients. Alcohol Clin Exp Res. 2012;36(3):406-16.

Lundbeck. Clinical study report 12013A. 2012a.

Lundbeck. Clinical study report 12014A. 2012b.

Lundbeck. Clinical study report 12023A. 2012c.

Lundbeck. Consequences of the reduction of alcohol consumption on quality of life with the use of nalmefene. 2012d.

Lundbeck. Summary of clinical efficacy report. 2012e.

Lundbeck. Alcohol dependence – Clinical practice in England. [Data on file 2014].

Luquiens A, Reynaud M, Falissard B, Aubin HJ. Quality of life among alcohol-dependent patients: how satisfactory are the available instruments? A systematic review. Drug Alcohol Depend. 2012;125(3):192-202.

MacDonald Z, Shields MA. Does problem drinking affect employment? Evidence from England. Health Econ. 2004:13(2):139-55.

Maisto SA, Sobell LC, Sobell MB. Comparison of alcoholics' self-reports of drinking behavior with reports of collateral informants. J Consult Clin Psychol. 1979;47(1):106-12.

Mann K, Bladström 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):706-13.

Marlatt GA, Witkiewitz K. (2002) Harm reduction approaches to alcohol use: health promotion, prevention, and treatment. Addict Behav. 27(6): 867-886.

Marques AC, Formigoni ML. Comparison of individual and group cognitive-behavioral therapy for alcohol and/or drug-dependent patients. Addiction. 2001 Jun;96(6):835-46.

McManus S, Meltzer H, Brugha T, Bebbington P, Jenkins R. Adult psychiatric morbidity in England, 2007: Results of a household survey. NHS Information Centre for Health and Social care, 2009.

Monti PM, Abrams DB, Binkoff JA, Zwick WR, Liepman MR, Nirenberg TD, et al. Communication skills training, communication skills training with family and cognitive behavioral mood management training for alcoholics. J Stud Alcohol. 1990 May;51(3):263-70.

Monti PM, Rohsenow DJ, Rubonis AV, Niaura RS, Sirota AD, Colby SM, et al. Cue exposure with coping skills treatment for male alcoholics: a preliminary investigation. J Consult Clin Psychol. 1993 Dec;61(6):1011-9.

Morgan MY, Landron F, Lehert P. Improvement in quality of life after treatment for alcohol dependence with acamprosate and psychosocial support. Alcohol Clin Exp Res. 2004;28(1):64-77.

Morgan TJ, Morgenstern J, Blanchard KA, Labouvie E, Bux DA. Health-related quality of life for adults participating in outpatient substance abuse treatment. Am J Addict. 2003;12(3):198-210.

Morgenstern J, Irwin TW, Wainberg ML, Parsons JT, Muench F, Bux DA Jr, 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 Feb;75(1):72-84.

Nalmefene (Selincro) [summary of product characteristics]. Valby, 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 22 January 2014.

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 22 January 2014.

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

National Institute for Health and Care Excellence (NICE). Alcohol-use disorders: diagnosis and clinical management of alcohol-related physical complications. 2010b. Available at: http://www.alcohollearningcentre.org.uk/pageFinder.cfm?cid=6052. Accessed 7 February 2014.

National Institute for Health and Care Excellence (NICE). Alcohol use disorders. The NICE guideline on diagnosis, assessment and management of harmful drinking and alcohol dependence. National clinical practice guideline 115. February 2011a. Available at: http://www.nice.org.uk/nicemedia/live/13337/53190/53190.pdf. Accessed 22 January 2014.

National Institute for Health and Care Excellence (NICE). NICE DSU technical support document 1: introduction to evidence synthesis for decision making. Dias S, Welton N, Sutton AJ, Ades AE. April 2011b. Available at: http://research-information.bris.ac.uk/explore/files/7215531/ TSD1_Introduction.final.08.05.12.pdf. Accessed 7 February 2014.

National Institute for Health and Care Excellence (NICE). National costing report: alcohol-use disorders: alcohol dependence. Costing report. Implementing NICE guidance. February 2011c. Available at: http://www.nice.org.uk/nicemedia/live/13337/53240/53240.pdf. Accessed 22 January 2014.

National Institute for Health and Care Excellence (NICE). Services for the identification and treatment of hazardous drinking, harmful drinking and alcohol dependence in children, young people and adults. Commissioning guide. August 2011d. Available at: http://www.nice.org.uk/media/331/CE/alcohol_v7.1_FINAL_PDF_Version_ update_111208.pdf. Accessed 27 February 2014.

National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. April 2013. Available at: http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyApprais al2013.pdf. Accessed 19 February 2014.

National Institute for Health and Care Excellence (NICE). Public Health Programme Guidance on Domestic Violence and Abuse—How Services Can Respond Effectively (PH50). 2014.Available at: http://guidance.nice.org.uk/PHG/Wave20/60. Accessed 20 February 2014.

Nestler EJ. Genes and addiction. Nat Genet. 2000;26(3):277-81.

Norstrom T, editor. Alcohol in postwar Europe consumption, drinking patterns, consequences and policy responses in 15 European countries. Almquiest & Wiksell Intl; 2002.

Office for National Statistics, Population Estimates for England and Wales, Mid-2011. 2011. Available at: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-england-and-wales/mid-2011--2011-census-based-/index.html. Accessed 19 February 2014.

Office for National Statistics. Deaths registered in England and Wales, 2012. 2013. Available at: http://www.ons.gov.uk/ons/rel/vsob1/death-reg-sum-tables/2012/sb-deaths-first-release--2012.html. Accessed 19 February 2014.

Orford J, Keddie A. Abstinence or controlled drinking in clinical practice: a test of the dependence and persuasion hypotheses. Br J Addict. 1986;81(4):495-504.

Peer K, Rennert L, Lynch KG, Farrer L, Gelernter J, Kranzler HR. Prevalence of DSM-IV and DSM-5 alcohol, cocaine, opioid, and cannabis use disorders in a largely substance dependent sample. Drug Alcohol Depend. 2013;127(1-3):215-9.

Personal Social Services Research Unit (PSSRU). Unit costs of health & social care 2012. 2012. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2012/index.php. Accessed 19 February 2014.

Petry NM, Martin B, Cooney JL, Kranzler HR. Give them prizes, and they will come: contingency management for treatment of alcohol dependence. J Consult Clin Psychol. 2000 Apr;68(2):250-7.

Pettinati HM, Weiss RD, Dundon W, Miller WR, Donovan D, Ernst DB, et al. A structured approach to medical management: a psychosocial intervention to support pharmacotherapy in the treatment of alcohol dependence. J Stud Alcohol Suppl. 2005;15:170-8.

Pettinati HM, Weiss RD, Miller WR, Donovan D, Ernst DB, Raunsaville BJ, editors. National Institute on Alcohol Abuse and Alcoholism. Medical management treatment manual. A clinical research guide for medically trained clinicians providing pharmacotherapy as part of the treatment for alcohol dependence. Bethesda, MD: US Department of Health and Human Services; 2004.

Pettinati HM, Gastfiend MD, Dong Q, Kranzler HR, O'Malley SS. Effect of extended-release naltrexone (XR-NTX) on quality of life in alcohol-dependent patients. Alcohol Clin Exp Res. 2009;33(2):350-6.

Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee; 2008.

Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess. 2004;8(36):iii-iv, ix-xi, 1-158.

Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. J Stud Alcohol. 1997 Jan;58(1):7-29.

Rehm J, Scafato E. Indicators of alcohol consumption and attributable harm for monitoring and surveillance in European Union countries. Addiction. 2011;106:4-10.

Rehm J, Gual A. Alcohol treatment policy and the AMPHORA project. 8 November 2013. Available at: http://www.addiction-ssa.org/RehmJ%20Amphora%20Final%20Nov%2013.ppt. Accessed 22 January 2014.

Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, et al. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet. 2009;373(9682):2223-33.

Rehm J, Roerecke M. Reduction of drinking in problem drinkers and all-cause mortality. Alcohol Alcohol. 2013;48(4):509-13.

Rehm J, Room R, Graham K, Monteiro M, Gmel G, Sempos CT. The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease: an overview. Addiction. 2003;98(9):1209-28.

Rehm J, Room R, Taylor B. Method for moderation: measuring lifetime risk of alcohol-attributable mortality as a basis for drinking guidelines. Int J Methods Psychiatr Res. 2008;17(3):141-51.

Rehm J, Shield KD. 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. Available at http://www.camh.ca/en/research/news_and_publications/reports_and_books/Documents/CAMH%20Alcohol%20Report%20Europe%202012.pdf. Accessed 22 January 2014.

Rehm J, Zatonksi W, Taylor B, Anderson P. Epidemiology and alcohol policy in Europe. Addiction. 2011;106(Suppl 1):11-9.

Roche AM, Pidd K, Berry JG, Harrison JE. Workers' drinking patterns: the impact on absenteeism in the Australian work-place. Addiction. 2008;103(5):738-48.

Rome AM. Psychosocial support for alcohol dependent patients (unpublished). 2014a.

Rome AM. Deconstructing BRENDA: an identification of the components of psychosocial support and their utility (unpublished). 2014b.

Rosenblum A, Foote J, Cleland C, Magura S, Mahmood D, Kosanke N. Moderators of effects of motivational enhancements to cognitive behavioral therapy. Am J Drug Alcohol Abuse. 2005a;31(1):35-58.

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

Sandahl C, Herlitz K, Ahlin G, Rönnberg S. Time-limited group psychotherapy for moderately alcohol dependent patients: a randomized controlled clinical trial. Psychother Res. 1998;8:361–78.

Scottish Intercollegiate Guideline Network (SIGN). The management of harmful drinking and alcohol dependence in primary care. September 2003. Available at: http://www.sign.ac.uk/pdf/sign74.pdf. Accessed 24 January 2014.

Scottish Medicines Consortium (SMC). Nalmefene (Selincro) advice. 2013. Available at: http://www.scottishmedicines.org.uk/SMC_Advice/Advice/917_13_nalmefene_Selincro/nalmefene_Selincro. Accessed 24 January 2014.

Sellman JD, Sullivan PF, Dore GM, Adamson SJ, MacEwan I. A randomized controlled trial of motivational enhancement therapy (MET) for mild to moderate alcohol dependence. J Stud Alcohol. 2001 May;62(3):389-96.

Shakeshaft AP, Bowman JA, Burrows S, Doran CM, Sanson-Fisher RW. Community-based alcohol counselling: a randomized clinical trial. Addiction. 2002 Nov;97(11):1449-63.

Sheffield University. 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. 2009. Available at: http://www.nice.org.uk/nicemedia/live/11828/45668/45668.pdf. Accessed 22 January 2014.

Shield KD. The alcohol relative risk functions and covariance matrices for long term diseases: version 2.1.6; 2011

Sinclair J, Chick J, Sørensen P, Kiefer F, Batel P, Gual A. Can Alcohol Dependent Patients Adhere to an 'As-Needed' Medication Regimen? Eur Addict Res. 2014 Feb 15;20(5):209-214.

Sisk JE, Whang W, Butler JC, Sneller VP, Whitney CG. Cost-effectiveness of vaccination against invasive pneumococcal disease among people 50 through 64 years of age: role of comorbid conditions and race. Ann Intern Med. 2003;138(12):960-8.

Sitharthan T, Sitharthan G, Hough MJ, Kavanagh DJ. Cue exposure in moderation drinking: a comparison with cognitive-behavior therapy. J Consult Clin Psychol. 1997 Oct;65(5):878-82.

Sobell LC, Sobell MB, Leo GI, Agrawal S, Johnson-Young L, Cunningham JA. Promoting self-change with alcohol abusers: a community-level mail intervention based on natural recovery studies. Alcohol Clin Exp Res. 2002 Jun;26(6):936-48.

Sobell LC, Sobell MB. 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):672-83.

Starosta AN, Leeman RF, Volpicelli JR. The BRENDA model: integrating psychosocial treatment and pharmacotherapy for the treatment of alcohol use disorders. J Psychiatr Pract. 2006;12(2):80-9.

Stevenson RJ, Lind B, Weatherburn D. The relationship between alcohol sales and assault in New South Wales, Australia. Addiction. 1999;94:397-410.

Taylor B, Rehm J, Room R, Patra J, Bondy S. Determination of lifetime injury mortality risk in Canada in 2002 by drinking amount per occasion and number of occasions. Am J Epidemiol. 2008;168(10):1119-25.

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.

Tolliver BK, Desantis SM, Brown DG, Prisciandaro JJ, Brady KT. A randomized, double-blind, placebo-controlled clinical trial of acamprosate in alcohol-dependent individuals with bipolar disorder: a preliminary report. Bipolar Disord. 2012;14(1):54-63.

UK Alcohol Treatment Trial (UKATT). Cost effectiveness of treatment for alcohol problems: findings of the randomised UK alcohol treatment trial (UKATT). BMJ. 2005;331(7516):544.

van Amsterdam J, van den Brink W. Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. J Psychopharmacol. 2013;27(11):987-97.

van den Brink W, Aubin HJ, Bladström 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):570-8.

van den Brink W, Aubin H-J, Bladström A, Torup L. Mann K, Gual A. ESENSE 1 - randomised controlled 6-month study of as-needed nalmefene: subgroup analysis of alcohol dependent patients with high drinking risk level. Eur Psychiatry. 2013;28 (Suppl 1): abstract 1107.

van den Brink W, Aubin H-J, Sørensen P, Torup L, Mann K, Gual A. ESENSE 2 - randomised controlled 6-month study of as-needed nalmefene: subgroup analysis of alcohol dependent patients with high drinking risk level. Eur Psychiatry. 2013;28 (Suppl 1): abstract 1108.

21st European Congress of Psychiatry Nice, France. 2013.

van den Brink W, Gual A, Mann K. White Paper: Reduction in alcohol consumption in the treatment of alcohol dependence. 13 February 2008.

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.

Vedel E, Emmelkamp PM, Schippers GM. 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):280-8.

Volpicelli JR, Pettinati HM, McLellan AT, O'Brien CP. Combining medication and psychosocial treatments for addictions: the BRENDA approach. New York: Guilford Press; 2001.

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.

Walitzer KS, Dermen KH. Alcohol-focused spouse involvement and behavioral couples therapy: evaluation of enhancements to drinking reduction treatment for male problem drinkers. J Consult Clin Psychol. 2004 Dec;72(6):944-55.

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

Weinreb RM, Van Horn DHA, Lynch KG, Lucey MR. A randomized, controlled study of treatment for alcohol dependence in patients awaiting liver transplantation. Liver Transplant. 2011;17(5):539-47.

World Health Organization (WHO). Global status report on alcohol and health. 2011. Available at: http://www.who.int/substance_abuse/publications/global_alcohol_report/en. Accessed 21 January 2014.

World Health Organization (WHO). Global status report on alcohol 2004. 2004. Available at: http://www.who.int/entity/substance_abuse/publications/globalstatusreportalcoholchapters/en. Accessed 21 January 2014.

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 22 January 2014.

World Health Organization (WHO). The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. 1992. Available at: http://www.who.int/classifications/icd/en/bluebook.pdf. Accessed 22 January 2014.

World Health Organization (WHO). The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. 1993. Available at: http://www.who.int/classifications/icd/en/GRNBOOK.pdf. Accessed 22 January 2014.

Yoon SJ, Pae CU, Kim DJ, Namkoong K, Lee E, et al. Mirtazapine for patients with alcohol dependence and comorbid depressive disorders: a multicentre, open label study. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(7):1196-201.

10 Appendices