Clinical trial results:
Interventional, open-label study of 18 mg Selincro® as needed use, in the treatment of patients with alcohol dependence in primary care

Summary

EudraCT number	2013-004688-30
Trial protocol	GB DE ES IT
Global end of trial date	11 February 2016

Results information

Result version number	v1 (current)
This version publication date	27 January 2017
First version publication date	27 January 2017

Trial information

Trial identification

Sponsor protocol code	15892A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02195817
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
Public contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, lundbeckClinicalTrials@lundbeck.com
Scientific contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, lundbeckClinicalTrials@lundbeck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2016
Global end of trial reached?	Yes
Global end of trial date	11 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the reduction in alcohol consumption in patients with alcohol dependence treated with 18 mg Selincro® as-needed use, in conjunction with continuous psychosocial support in primary care (Cohort A).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice (1996)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 84
Country: Number of subjects enrolled	United Kingdom: 97
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 106
Worldwide total number of subjects	330
EEA total number of subjects	330

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	285
From 65 to 84 years	45

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Cohort A comprised patients who maintained a high drinking risk level (DRL) in the period between the Screening and Inclusion Visits. Cohort B comprised patients who reduced their alcohol consumption (therefore not eligible for Selincro® treatment). No data is reported from the observational cohort (B)

Period 1

Period 1 title	Cohort A (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Cohort A

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Nalmefene
Investigational medicinal product code	
Other name	Selincro (R)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

18mg; as needed; tablets, orally

Number of subjects in period 1	Cohort A
Started	330
Completed	268
Not completed	62
Withdrawal of Consent	21
Adverse event, non-fatal	18
Lost to follow-up	6
Non-compliance with IMP	3
Administrative or other reason(s)	7
Lack of efficacy	1
Protocol deviation	6

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A

Reporting group description: -

Reporting group values	Cohort A	Total	
Number of subjects	330	330	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	285	285	
From 65-84 years	45	45	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	51.98		
standard deviation	± 11.25	-	
Gender categorical Units: Subjects			
Female	114	114	
Male	216	216	
Race Units: Subjects			
White	328	328	
Black Or African American	1	1	
Other	1	1	

End points

End points reporting groups

Reporting group title	Cohort A
Reporting group description: -	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who had at least one valid post-inclusion assessment of the primary efficacy variable (HDDs)	
Subject analysis set title	Month 3
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients at week 12 who had at least one valid post-inclusion assessment of the primary efficacy variable (HDDs)	

Primary: Change in the number of HDDs (days/month)

End point title	Change in the number of HDDs (days/month)
End point description:	
End point type	Primary
End point timeframe:	
Baseline to Month 3	

End point values	Baseline	Month 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	301	262		
Units: days/month				
arithmetic mean (standard deviation)	24.14 (± 5.09)	11.22 (± 10.1)		

Statistical analyses

Statistical analysis title	Change from Baseline to Month 3 in number of HDD
Statistical analysis description:	
Mixed model for repeated measurement, using all available observations until completion or withdrawal from the study. The model included sex, site, and time in months (Months 1 to 3) as fixed categorical effects, baseline number of HDDs as a continuous covariate, and baseline number of HDDs-by-month interaction. An unstructured covariance structure was used to model the within-patient errors and the estimation method used a restricted maximum likelihood (REML)-based approach	
Comparison groups	Baseline v Month 3
Number of subjects included in analysis	563
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-13.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.4
upper limit	-11.9

Secondary: Change on monthly Total Alcohol Consumption (TAC)

End point title	Change on monthly Total Alcohol Consumption (TAC)

End point description:

End point type	Secondary

End point timeframe:

Baseline to Month 3

End point values	Baseline	Month 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	301	262		
Units: g/day				
arithmetic mean (standard deviation)	111.23 (± 53.02)	49.55 (± 42.03)		

Statistical analyses

Statistical analysis title	Adjusted Change in Total Alcohol Consumption (TAC)

Statistical analysis description:

Mixed model for repeated measurement, using all available observations until completion or withdrawal from the study. The model included sex, site, and time in months (Months 1 to 3) as fixed categorical effects, baseline TAC as a continuous covariate, and baseline TAC-by-month interaction. An unstructured covariance structure was used to model the within-patient errors and the estimation method used a restricted maximum likelihood (REML)-based approach

Comparison groups	Baseline v Month 3
Number of subjects included in analysis	563
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-69.4
upper limit	-58.6

Secondary: Response Shift Drinking Risk Level (RSDRL)

End point title	Response Shift Drinking Risk Level (RSDRL)

End point description:

Defined as a downward shift from baseline in drinking risk level (DRL); for patients with a very high DRL at baseline, a shift to medium DRL or lower; for patients with a high DRL at baseline, a shift to low DRL or below

End point type	Secondary

End point timeframe:

Baseline to month 3

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	262			
Units: percentage (%)				
number (confidence interval 95%)	55.3 (49.3 to 61.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response Low Drinking Risk Level (RLDRL)

End point title	Response Low Drinking Risk Level (RLDRL)

End point description:

Defined as a downward shift from baseline to Month 3 in DRL; for patients at very high risk at baseline: a shift to medium risk or lower, and for patients at high risk at baseline: a shift to low risk or lower)

End point type	Secondary

End point timeframe:

Baseline and month 3

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	262			
Units: percentage (%)				
number (confidence interval 95%)	43.9 (38 to 49.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response defined as ≥70% reduction in TAC

End point title	Response defined as ≥70% reduction in TAC

End point description:

End point type	Secondary

End point timeframe:
baseline to Month 3

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	262			
Units: percentage				
number (confidence interval 95%)	37.4 (31.8 to 43.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response defined as ≥50% reduction in TAC

End point title	Response defined as ≥50% reduction in TAC

End point description:

End point type	Secondary

End point timeframe:
Baseline to month 3

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	262			
Units: Percentage				
number (confidence interval 95%)	61.1 (55 to 66.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response defined as 0 to 4 HDDs (days/month)

End point title	Response defined as 0 to 4 HDDs (days/month)

End point description:

End point type	Secondary

End point timeframe:

Month 3

End point values	Month 3			
Subject group type	Subject analysis set			
Number of subjects analysed	262			
Units: percentage				
number (confidence interval 95%)	37.8 (32.1 to 43.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Clinical Global Impression, Severity of illness (CGI-S)

End point title	Change from baseline in Clinical Global Impression, Severity of illness (CGI-S)

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Baseline	Month 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	301	265		
Units: Scale				
arithmetic mean (standard deviation)	4.01 (± 0.95)	2.83 (± 1.08)		

Statistical analyses

Statistical analysis title	Adjusted Change from Baseline to week 12

Statistical analysis description:

Mixed model for repeated measurement, using all available observations until completion or withdrawal from the study. The model included sex, site, and time in months (Months 1 to 3) as fixed categorical effects, baseline CGI-S as a continuous covariate, and baseline CGI-S-by-month interaction. An unstructured covariance structure was used to model the within-patient errors and the estimation method used a restricted maximum likelihood (REML)-based approach

Comparison groups	Baseline v Month 3
Number of subjects included in analysis	566
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-1.1

Secondary: Clinical Global Impression, global improvement (CGI-I)

End point title	Clinical Global Impression, global improvement (CGI-I)
End point description:	
A 7-point scale ranging from 1 (Normal - not at all ill) to 7 (among the most extremely ill patients).	
End point type	Secondary
End point timeframe:	
Weeks 12	

End point values	Month 3			
Subject group type	Subject analysis set			
Number of subjects analysed	265			
Units: score				
arithmetic mean (standard deviation)	2.51 (± 0.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Liver function (γ-glutamyl transferase (γGT))

End point title	Liver function (γ-glutamyl transferase (γGT))
End point description:	
Liver function was evaluated by measurement of transaminases, γ-glutamyl transferase (γGT)	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Baseline	Month 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	301	235		
Units: U/L				
geometric mean (standard deviation)	69.55 (± 153.66)	60.09 (± 176.74)		

Statistical analyses

Statistical analysis title	Change from Baseline in γGT

Statistical analysis description:

Mixed model for repeated measurement, using all available observations until completion or withdrawal from the study. The model included sex, site, and time in months (Months 1 to 3) as fixed categorical effects, baseline γGT as a continuous covariate, and baseline number of γGT-by-month interaction. An unstructured covariance structure was used to model the within-patient errors and the estimation method used a restricted maximum likelihood (REML)-based approach

Comparison groups	Baseline v Month 3
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	0.95

Secondary: Liver function (alanine aminotransferase (ALT)

End point title	Liver function (alanine aminotransferase (ALT)

End point description:

Liver function was evaluated by measurement of alanine aminotransferase (ALT)

End point type	Secondary

End point timeframe:

week 12

End point values	Baseline	Month 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	301	231		
Units: IU/L				
geometric mean (standard deviation)	29.22 (± 23.71)	26.44 (± 20.41)		

Statistical analyses

Statistical analysis title	Change from Baseline in ALT

Statistical analysis description:

Mixed model for repeated measurement, using all available observations until completion or withdrawal from the study. The model included sex, site, and time in months (Months 1 to 3) as fixed categorical effects, baseline ALT as a continuous covariate, and ALT-by-month interaction. An unstructured covariance structure was used to model the within-patient errors and the estimation method used a restricted maximum likelihood (REML)-based approach

Comparison groups	Baseline v Month 3
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	0.97

Secondary: Liver function (aspartate aminotransferase (AST))

End point title	Liver function (aspartate aminotransferase (AST))

End point description:

End point type	Secondary

End point timeframe:

week 12

End point values	Baseline	Month 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	300	231		
Units: U/L				
geometric mean (standard deviation)	32.17 (± 32.32)	28.52 (± 33.46)		

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in AST

Statistical analysis description:

Mixed model for repeated measurement, using all available observations until completion or withdrawal from the study. The model included sex, site, and time in months (Months 1 to 3) as fixed categorical effects, baseline AST as a continuous covariate, and baseline AST-by-month interaction. An unstructured covariance structure was used to model the within-patient errors and the estimation method used a restricted maximum likelihood (REML)-based approach

Comparison groups	Baseline v Month 3
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	0.95

Secondary: Change in the Short-Form 36-Item Health Survey (SF-36): physical

End point title	Change in the Short-Form 36-Item Health Survey (SF-36): physical

End point description:

The scores range from 0 to 100, with higher scores indicating better quality of life

End point type	Secondary

End point timeframe:

baseline to week 12

End point values	Baseline	Month 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123	123		
Units: Scale				
arithmetic mean (standard deviation)	44.9 (± 9.83)	46.94 (± 9.79)		

Statistical analyses

Statistical analysis title	Change from Baseline in SF-36 Physical Component

Statistical analysis description:

Analysed using an ANCOVA model with missing values imputed by last observation carried forward (LOCF), including sex and site as fixed effects, and baseline score as a covariate

Comparison groups	Baseline v Month 3

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	3.9

Secondary: Change in the Short-Form 36-Item Health Survey (SF-36): Mental component

End point title	Change in the Short-Form 36-Item Health Survey (SF-36): Mental component
End point description:	
The scores range from 0 to 100, with higher scores indicating better quality of life	
End point type	Secondary
End point timeframe:	
baseline to week 12	

End point values	Baseline	Month 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123	123		
Units: Scale				
arithmetic mean (standard deviation)	31.76 (± 13.15)	38.98 (± 14.28)		

Statistical analyses

Statistical analysis title	Change from Baseline in SF-36 Mentall Component
Statistical analysis description:	
Analysed using an ANCOVA model with missing values imputed by last observation carried forward (LOCF), including sex and site as fixed effects, and baseline score as a covariate	
Comparison groups	Baseline v Month 3
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.9
upper limit	10.5

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
First dose to follow-up	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	COHORT A
Reporting group description:	
COHORT A	

Serious adverse events	COHORT A		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 311 (7.07%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Presyncope			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	2 / 311 (0.64%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	2 / 311 (0.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium tremens			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Depressive symptom			
subjects affected / exposed	2 / 311 (0.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Flight of ideas			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Impulsive behaviour			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mood swings			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Suicide attempt			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	COHORT A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 311 (37.94%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	55 / 311 (17.68%)		
occurrences (all)	71		
Headache			
subjects affected / exposed	24 / 311 (7.72%)		
occurrences (all)	27		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	57 / 311 (18.33%)		
occurrences (all)	66		
Vomiting			
subjects affected / exposed	19 / 311 (6.11%)		
occurrences (all)	23		
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	33 / 311 (10.61%) 37		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 September 2015	The study was terminated due to enrolment challenges	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated due to enrolment challenges

Notes: