Clinical trial results:
Exploratory, interventional, open-label, fixed-dose study with Selincro® as-needed use, in alcohol dependent patients with liver impairment

Summary

EudraCT number	2014-000413-31
Trial protocol	DE
Global end of trial date	03 December 2015

Results information

Result version number	v1 (current)
This version publication date	11 December 2016
First version publication date	11 December 2016

Trial information

Trial identification

Sponsor protocol code	15871A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02197598
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, +45 36301311, LundbeckClinicalTrials@lundbeck.com
Scientific contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, +45 36301311, 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	03 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2015
Global end of trial reached?	Yes
Global end of trial date	03 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Exploratory objectives to be assessed in patients with alcohol dependence and liver impairment treated with 18 mg Selincro® (nalmefene), as-needed, over 12 weeks:
- To explore the reduction of alcohol consumption
- To explore the change in liver stiffness
- To explore the change in Controlled Attenuation Parameter (CAP)
- To explore the change in liver enzymes
- To explore the shift in fibrosis stage
- To explore the associations between reduction of alcohol consumption, liver stiffness, CAP and liver enzymes

To explore the change in patients with alcohol dependence and liver impairment treated with 18 mg Selincro® (nalmefene), as-needed, on:
- Clinical Global Impression
- Quality of life

Safety objective:
To evaluate safety and tolerability of 18 mg Selincro® (nalmefene), as-needed, in patients with alcohol dependence and liver impairment

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	17 September 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	Germany: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	34
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who met each of the inclusion and none of the exclusion criteria were eligible to participate in the study

Period 1

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

Arms

Arm title	Nalmefene

Arm description:

One tablet orally for 12 weeks on days when the patient perceives a risk of drinking alcohol, preferably 1-2 hours prior to the anticipated risk of drinking

Arm type	Experimental
Investigational medicinal product name	nalmefene
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

18mg, as needed; tablets, orally

Number of subjects in period 1	Nalmefene
Started	45
Completed	39
Not completed	6
Consent withdrawn by subject	2
Adverse event, non-fatal	2
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	45	45	
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)	34	34	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	59.5		
standard deviation	± 8	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	25	25	
Race Units: Subjects			
White	45	45	

End points

End points reporting groups

Reporting group title	Nalmefene
Reporting group description: One tablet orally for 12 weeks on days when the patient perceives a risk of drinking alcohol, preferably 1-2 hours prior to the anticipated risk of drinking	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description: Nalmefene, baseline	
Subject analysis set title	Week 1
Subject analysis set type	Full analysis
Subject analysis set description: Nalmefene week 1	
Subject analysis set title	Week 2
Subject analysis set type	Full analysis
Subject analysis set description: nalmefene week 2	
Subject analysis set title	Month 1
Subject analysis set type	Full analysis
Subject analysis set description: Nalmefene week 4	
Subject analysis set title	Month 2
Subject analysis set type	Full analysis
Subject analysis set description: nalmefene week 8	
Subject analysis set title	Month 3
Subject analysis set type	Full analysis
Subject analysis set description: Nalmefene week 12	
Subject analysis set title	Screening
Subject analysis set type	Full analysis
Subject analysis set description: Screening	
Subject analysis set title	Better Fibrosis Stage at week 12
Subject analysis set type	Full analysis
Subject analysis set description: Better Fibrosis Stage at week 12	
Subject analysis set title	Worse Fibrosis Stage at week 12
Subject analysis set type	Full analysis
Subject analysis set description: Worse fibrosis stage at week 12	

Primary: Change from baseline in the number of heavy drinking days per month (HDDs)

End point title	Change from baseline in the number of heavy drinking days per month (HDDs)
End point description:	
End point type	Primary

End point timeframe:

Baseline to month 1 and 2, and 3

End point values	Baseline	Month 1	Month 2	Month 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	44	44	40	39
Units: days/month				
arithmetic mean (standard error)	26.14 (± 0.42)	13.74 (± 1.44)	13.08 (± 1.61)	12.92 (± 1.72)

Statistical analyses

Statistical analysis title	Adjusted Change from Baseline to Month 1

Statistical analysis description:

Change from baseline in number of HDDs analysed using a mixed model for repeated measurements using all available data until withdrawal from study, with sex, site, and time in months as fixed factors, and the baseline value as a covariate. The baseline value-by time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. Least squares means for the change from baseline in number of HDDs was presented with two-sided 95% CIs

Comparison groups	Month 1 v Baseline
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-12.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.5
upper limit	-9.8

Statistical analysis title	Adjusted Change from Baseline to Month 2

Statistical analysis description:

Change from baseline in number of HDDs analysed using a mixed model for repeated measurements using all available data until withdrawal from study, with sex, site, and time in months as fixed factors, and the baseline value as a covariate. The baseline value-by time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. Least squares means for the change from baseline in number of HDDs was presented with two-sided 95% CIs

Comparison groups	Baseline v Month 2
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-13.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.2
upper limit	-10.1

Statistical analysis title	Adjusted Change from Baseline to Month 3

Statistical analysis description:

Change from baseline in number of HDDs analysed using a mixed model for repeated measurements using all available data until withdrawal from study, with sex, site, and time in months as fixed factors, and the baseline value as a covariate. The baseline value-by time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. Least squares means for the change from baseline in number of HDDs was presented with two-sided 95% CIs

Comparison groups	Baseline v Month 3
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-13.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.8
upper limit	-10.2

Primary: Change from baseline in weekly number of HDDs

End point title	Change from baseline in weekly number of HDDs[1]

End point description:

End point type	Primary

End point timeframe:

Baseline to weeks 1 and 2

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Week 1	Week 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: days/week				
arithmetic mean (standard error)	-2.76 (± 0.37)	-3.21 (± 0.41)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Monthly Total Alcohol Consumption (TAC)

End point title	Change from Baseline in Monthly Total Alcohol Consumption (TAC)

End point description:

End point type	Primary

End point timeframe:

baseline, months 1, 2 and 3

End point values	Baseline	Month 1	Month 2	Month 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45	44	40	39
Units: g/day				
arithmetic mean (standard error)	98.33 (± 6.2)	56.73 (± 6.23)	57.28 (± 6.65)	54.95 (± 6.75)

Statistical analyses

Statistical analysis title	Adjusted Change from Baseline to Month 1

Statistical analysis description:

Change from baseline in TAC analysed using a mixed model for repeated measurements (MMRM) using all available data until withdrawal from study, with sex, site, and time in months as fixed factors, and the baseline value as a covariate. The baseline value-by time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. Least squares means for the change from baseline in TAC was presented with two-sided 95% CI

Comparison groups	Baseline v Month 1
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-42.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.4
upper limit	-31.4

Statistical analysis title	Adjusted Change from Baseline to Month 3

Statistical analysis description:

Change from baseline in TAC analysed using a mixed model for repeated measurements (MMRM) using all available data until withdrawal from study, with sex, site, and time in months as fixed factors, and the baseline value as a covariate. The baseline value-by time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. Least squares means for the change from baseline in TAC was presented with two-sided 95% CI

Comparison groups	Baseline v Month 3

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-45.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.6
upper limit	-33

Statistical analysis title	Adjusted Change from Baseline to Month 2

Statistical analysis description:

Change from baseline in TAC analysed using a mixed model for repeated measurements (MMRM) using all available data until withdrawal from study, with sex, site, and time in months as fixed factors, and the baseline value as a covariate. The baseline value-by time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. Least squares means for the change from baseline in TAC was presented with two-sided 95% CI

Comparison groups	Baseline v Month 2
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-42.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.2
upper limit	-31.5

Primary: Change from Baseline in Weekly TAC

End point title	Change from Baseline in Weekly TAC[2]

End point description:

End point type	Primary

End point timeframe:

Baseline, Week 1 and 2

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Week 1	Week 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: g/day				
arithmetic mean (standard error)	-39.2 (± 6.2)	-44.56 (± 6.29)		

Statistical analyses

No statistical analyses for this end point

Primary: Response Shift Drinking Risk Level (RSDRL)

End point title	Response Shift Drinking Risk Level (RSDRL)[3]

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	Primary

End point timeframe:

Baseline to month 3

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Nalmefene			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: percentage (%)				
number (confidence interval 95%)	38.5 (24.9 to 54.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Response Low Drinking Risk Level (RLDRL)

End point title	Response Low Drinking Risk Level (RLDRL)[4]

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	Primary

End point timeframe:

Baseline and month 3

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Nalmefene			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: percentage				
number (confidence interval 95%)	33.3 (20.6 to 49)			

Statistical analyses

No statistical analyses for this end point

Primary: Response defined as ≥50% reduction in TAC

End point title	Response defined as ≥50% reduction in TAC[5]

End point description:

End point type	Primary

End point timeframe:

baseline to month 3

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Nalmefene			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: percentage				
number (confidence interval 95%)	48.7 (33.9 to 63.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Response defined as ≥70% reduction in TAC

End point title	Response defined as ≥70% reduction in TAC[6]

End point description:

End point type	Primary

End point timeframe:

baseline to Month 3

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Nalmefene			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: percentage				
number (confidence interval 95%)	23.1 (12.6 to 38.3)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Response defined as 0 to 4 HDDs (days/month)[7]

End point description:

End point type	Primary

End point timeframe:

Month 3

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Nalmefene			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: percentage				
number (confidence interval 95%)	30.8 (18.6 to 46.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Liver stiffness

End point title	Liver stiffness

End point description:

End point type	Primary

End point timeframe:

Baseline to weeks 1,2 4 and 12

End point values	Baseline	Week 1	Week 2	Month 1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	44	42	40	42
Units: kPa				
geometric mean (standard deviation)	6.17 (± 2.02)	6.43 (± 2.07)	6.47 (± 2.04)	6.37 (± 1.96)

End point values	Month 3	Screening		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	45		
Units: kPa				
geometric mean (standard deviation)	6.3 (± 2.2)	7.04 (± 2.18)		

Statistical analyses

Statistical analysis title	Liver Stiffness: Screening vs baseline

Statistical analysis description:

The log-transformed value of liver stiffness was analysed using an MMRM model with sex, site, and time in weeks as fixed factors, and the log-transformed baseline score as a covariate. The log-transformed baseline value-by-time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. The adjusted mean was back-transformed using the exponential function and presented as geometric mean

Comparison groups	Screening v Baseline
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	6.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.37
upper limit	7.34

Statistical analysis title	Liver Stiffness: Screening vs week 1

Statistical analysis description:

The log-transformed value of liver stiffness was analysed using an MMRM model with sex, site, and time in weeks as fixed factors, and the log-transformed baseline score as a covariate. The log-transformed baseline value-by-time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. The adjusted mean was back-transformed using the exponential function and presented as geometric mean

Comparison groups	Screening v Week 1

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	6.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.41
upper limit	7.08

Statistical analysis title	Liver Stiffness: Screening vs week 2

Statistical analysis description:

The log-transformed value of liver stiffness was analysed using an MMRM model with sex, site, and time in weeks as fixed factors, and the log-transformed baseline score as a covariate. The log-transformed baseline value-by-time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. The adjusted mean was back-transformed using the exponential function and presented as geometric mean

Comparison groups	Screening v Week 2
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	6.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.57
upper limit	7.54

Statistical analysis title	Liver Stiffness: Screening vs week 4

Statistical analysis description:

The log-transformed value of liver stiffness was analysed using an MMRM model with sex, site, and time in weeks as fixed factors, and the log-transformed baseline score as a covariate. The log-transformed baseline value-by-time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. The adjusted mean was back-transformed using the exponential function and presented as geometric mean

Comparison groups	Screening v Month 1
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	6.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.51
upper limit	7.16

Statistical analysis title	Liver Stiffness: Screening vs week 12

Statistical analysis description:

The log-transformed value of liver stiffness was analysed using an MMRM model with sex, site, and time in weeks as fixed factors, and the log-transformed baseline score as a covariate. The log-transformed baseline value-by-time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. The adjusted mean was back-transformed using the exponential function and presented as geometric mean

Comparison groups	Screening v Month 3
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.02
upper limit	7.18

Primary: Category shift in fibrosis stage

End point title	Category shift in fibrosis stage[8]

End point description:

In general, the fibrosis stage remained unchanged in the majority of the patients at Month 3. A total of 8 patients shifted to a lower (better) fibrosis stage at Month 3: 4 patients shifted from stage F1-2 to F0, 3 patients shifted from stage F3 to F1-2 or F0, and 1 patient shifted from stage F4 to F0. A total of 5 patients shifted to a higher (worse) fibrosis stage at Month 3: 2 patients shifted from stage F0 to F1-2, 2 patients shifted from stage F1-2 to F3, and 1 patient shifted from stage F3 to F4.

End point type	Primary

End point timeframe:

Baseline to weeks 1,2 4, and 12

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Better Fibrosis Stage at week 12	Worse Fibrosis Stage at week 12		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	39		
Units: Number of subjects	8	5		

Statistical analyses

No statistical analyses for this end point

Primary: The therapeutic effect on the change in controlled attenuation parameter (CAP)

End point title	The therapeutic effect on the change in controlled attenuation parameter (CAP)

End point description:

The therapeutic effect on the change in controlled attenuation parameter (CAP)

End point type	Primary

End point timeframe:

to week 12

End point values	Month 3	Screening		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	45		
Units: dB/m				
geometric mean (standard deviation)	266.52 (± 1.27)	295.2 (± 1.17)		

Statistical analyses

Statistical analysis title	Change from screening to week 12

Statistical analysis description:

Analysed using a mixed model for repeated measurements (MMRM) using all available data until withdrawal from study, with sex, site, and time in weeks as fixed factors, and the baseline value as a covariate. The baseline value-by time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. Least squares means for the change from baseline was presented with two-sided 95% confidence intervals (CIs).

Comparison groups	Month 3 v Screening
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	264.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	247.96
upper limit	283

Primary: Liver function

End point title	Liver function

End point description:

Liver function was evaluated by measurement of transaminases, γ-glutamyl transferase (γGT), change from baseline in bilirubin, albumin, and International Normalized Ratio (INR). The mean values of bilirubin, albumin, and INR were unchanged at Month 3, so only γ-glutamyl transferase (γGT) are presented

End point type	Primary

End point timeframe:
Baseline to weeks 1,2,4,8, and 12

End point values	Week 1	Week 2	Month 1	Month 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	42	42	39
Units: IU/L				
geometric mean (standard deviation)	65.99 (± 3.34)	62.67 (± 3.23)	55.77 (± 2.98)	61.88 (± 3.34)

End point values	Month 3	Screening		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	45		
Units: IU/L				
geometric mean (standard deviation)	62.59 (± 3.41)	72.51 (± 3.14)		

Statistical analyses

Statistical analysis title	screening vs week 12
Comparison groups	Month 3 v Screening
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	geometric mean
Point estimate	60.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	48.96
upper limit	74.21

Primary: 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	Primary

End point timeframe:
Baseline to weeks 4 and 12

End point values	Baseline	Month 1	Month 3	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	45	42	39	
Units: Scale				
arithmetic mean (standard deviation)	3.89 (± 0.93)	3.02 (± 1.05)	2.74 (± 0.91)	

Statistical analyses

Statistical analysis title	Adjusted Change from Baseline to week 4
Comparison groups	Baseline v Month 1
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.5

Statistical analysis title	Adjusted Change from Baseline to week 12
Comparison groups	Baseline v Month 3
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.7

Primary: Clinical Global Impression, global improvement (CGI-I)	
End point title	Clinical Global Impression, global improvement (CGI-I)[9]
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	Primary

End point timeframe:

Weeks 4 and 12

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Month 1	Month 3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	39		
Units: score				
arithmetic mean (standard deviation)	2.83 (± 0.91)	2.67 (± 0.93)		

Statistical analyses

No statistical analyses for this end point

Primary: 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[10]

End point description:

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

End point type	Primary

End point timeframe:

week 12

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Month 3	Screening		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	45		
Units: Scale				
arithmetic mean (standard deviation)	47.52 (± 11.41)	42.66 (± 13.7)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in the Short-Form 36-Item Health Survey (SF-36): physical component[11]

End point description:

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

End point type	Primary

End point timeframe:

week 12

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Summerised using descriptive statistics

End point values	Month 3	Screening		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	45		
Units: Scale				
arithmetic mean (standard deviation)	52.76 (± 6.44)	51.58 (± 7.18)		

Statistical analyses

No statistical analyses for this end point

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	16.1

Reporting groups	
Reporting group title	NALMEFENE
Reporting group description:	
NALMEFENE	

Serious adverse events	NALMEFENE		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 45 (6.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Alcohol detoxification			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	NALMEFENE		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 45 (68.89%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 45 (31.11%)		
occurrences (all)	14		
Headache			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	9		
Paraesthesia			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	6		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	9		
Malaise			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Dyshidrotic eczema			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Restlessness subjects affected / exposed occurrences (all)	 9 / 45 (20.00%) 9 5 / 45 (11.11%) 5		

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? No

Limitations and caveats

None reported