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Protocol Registration and Results System

ID: 12013A Safety and Efficacy of Nalmefene in Patients With Alcohol Dependence NCT00811941

Protocol Registration and Results Preview

Close

Safety and Efficacy of Nalmefene in Patients With Alcohol Dependence (SENSE)

This study has been completed.

Sponsor:	H. Lundbeck A/S
Collaborators:	
Information provided by (Responsible Party):	H. Lundbeck A/S
ClinicalTrials.gov Identifier:	NCT00811941

Purpose

The purpose of the study is long-term safety, tolerability and efficacy of nalmefene in patients with alcohol dependence.

Condition	Intervention	Phase
Alcohol Dependence	Drug: Placebo Drug: Nalmefene	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study

Official Title: A 52-week, Randomised, Double-blind, Placebo-controlled, Parallel-group, Safety, Tolerability and Efficacy Study of Nalmefene, as Needed Use, in Patients With Alcohol Dependence

Further study details as provided by H. Lundbeck A/S:

Primary Outcome Measure:

- Number of Patients With Adverse Events (AEs) [Time Frame: Serious Adverse Events: 52 weeks and a safety follow-up (visit/telephone call) scheduled for 4 weeks after completion of the study or after withdrawal from the study. Other Adverse Events: 52 weeks.] [Designated as safety issue: Yes]
  Overview of AEs

- Percentage of Patients Who Withdrew Due to Intolerance to Treatment [Time Frame: Baseline to Week 52] [Designated as safety issue: Yes]

- Change From Baseline in the Monthly Number of Heavy Drinking Days (HDDs) [Time Frame: Baseline and Month 6] [Designated as safety issue: No]

Number of HDDs over a month (28 days), where one HDD was defined as a day with alcohol consumption ≥60 grams (g) for men and ≥40 g for women.

- Change From Baseline in the Monthly Total Alcohol Consumption (TAC) [Time Frame: Baseline and Month 6] [Designated as safety issue: No]
  TAC was defined as mean daily alcohol consumption in g/day over a month (28 days).

Secondary Outcome Measures:

- Drinking Risk Level (RSDRL) Response [Time Frame: Month 6] [Designated as safety issue: No]
  RSDRL response was defined as a downward shift from baseline in Drinking Risk Level (DRL); 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.

- Change From Baseline in Clinical Status Using CGI-S [Time Frame: Baseline and Week 24] [Designated as safety issue: No]
  The Clinical Global Impression - Severity of Illness (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).

- Change in Clinical Status Using the CGI-I [Time Frame: Week 24] [Designated as safety issue: No]
  The Clinical Global Impression - Global Improvement (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).

- Liver Function Test Gamma-glutamyl Transferase (GGT) [Time Frame: Week 24] [Designated as safety issue: No]
  GGT values

- Liver Function Test Alanine Aminotransferase (ALAT) [Time Frame: Week 24] [Designated as safety issue: No]
  ALAT values

- Change From Baseline in the Monthly Number of Heavy Drinking Days (HDDs) [Time Frame: Baseline and Month 13] [Designated as safety issue: No]
  Number of HDDs over a month (28 days), where one HDD was defined as a day with alcohol consumption ≥60 g for men and ≥40 g for women.

- Change From Baseline in the Monthly Total Alcohol Consumption (TAC) [Time Frame: Baseline and Month 13] [Designated as safety issue: No]
  TAC was defined as mean daily alcohol consumption in g/day over a month (28 days).

- Drinking Risk Level (RSDRL) Response [Time Frame: Month 13] [Designated as safety issue: No]
  RSDRL response was defined as a downward shift from baseline in Drinking Risk

Level (DRL); 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.

- Change From Baseline in Clinical Status Using CGI-S [Time Frame: Baseline and Week 52] [Designated as safety issue: No]
  The Clinical Global Impression - Severity of Illness (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).

- Change in Clinical Status Using the CGI-I [Time Frame: Week 52] [Designated as safety issue: No]
  The Clinical Global Impression - Global Improvement (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).

- Liver Function Test Gamma-glutamyl Transferase (GGT) [Time Frame: Week 52] [Designated as safety issue: No]
  GGT values

- Liver Function Test Alanine Aminotransferase (ALAT) [Time Frame: Week 52] [Designated as safety issue: No]
  ALAT values

Enrollment: 665
Study Start Date: March 2009
Study Completion Date: November 2010
Primary Completion Date: November 2010

Arms	Assigned Interventions
Placebo Comparator: Placebo	Drug: Placebo as-needed use, tablets, orally, 52 weeks
Experimental: Nalmefene	Drug: Nalmefene 18.06 mg as-needed use, tablets, orally, 52 weeks. 18.06 mg nalmefene equals 20 mg nalmefene hydrochloride. Other Names: • Selincro™

Alcohol dependence is a maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by at least three of a number of criteria such as tolerance, withdrawal symptoms, frequent use of alcohol in larger amounts or over longer periods than was intended, and others. Excessive intake of alcohol reduces the life span by a decade, and alcohol drinking is strongly related to mortality from liver cirrhosis, chronic pancreatitis, certain cancers, hypertension, accidents and violence. This study is planned to evaluate the long-term safety and tolerability as well as to evaluate the efficacy of as needed use of 18.06 mg nalmefene in patients with alcohol dependence.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Inclusion Criteria:

In- and outpatients who:

- had a primary diagnosis of alcohol dependence according to Diagnostic and Statistical Manual of Mental Disorders - text revision (DSM-IV-TR) criteria
- had had ≥6 Heavy Drinking Days (HDDs) in the 4 weeks preceding the Screening Visit

Exclusion Criteria:

The patient:

- had a severe psychiatric disorder or an antisocial personality disorder
- had risk of suicide evaluated by the suicidality module of the Mini-International Neuropsychiatric Interview (MINI)
- had a history of delirium tremens or alcohol withdrawal seizures
- reported current or recent (within 3 months preceding screening) treatment with disulfiram, acamprosate, topiramate, naltrexone or carbimide, or with any opioid antagonists
- was pregnant or breast-feeding

Other protocol-defined inclusion and exclusion criteria may apply.

Contacts and Locations

Locations

Czech Republic

CZ007
Litomerice, Czech Republic, 412 01
CZ006
Lnare, Czech Republic, 38742
CZ005
Prague, Czech Republic, 100 00
CZ004
Praha 6, Czech Republic, 160 00
CZ001
Usti nad Labem, Czech Republic, 400 13

Estonia

EE002
Parnu, Estonia, 80012
EE004
Tallinn, Estonia, 10613
EE005
Tallinn, Estonia, 10613
EE001
Voru, Estonia, 65608
EE003

Vorumaa, Estonia, 65526

Hungary

HU002

Budapest, Hungary, 1163

HU004

Budapest, Hungary, 1135

Latvia

LV003

Daugavpils, Latvia, 5403

LV002

Jelgava, Latvia, 3008

LV001

Riga, Latvia, 1013

LV004

Sigulda, Latvia, 2150

Lithuania

LT002

Kaunas, Lithuania, 44184

LT003

Kaunas, Lithuania, 50185

Poland

PL015

Belchatow, Poland, 97-400

PL008

Bydgoszcz, Poland, 85-096

PL006

Gdansk, Poland, 80-211

PL011

Krakow, Poland, 31-826

PL002

Leszno, Poland, 64-100

PL010

Lodz, Poland, 91-229

PL014

Lodz, Poland, 91-229

PL004

Lublin, Poland, 20-015

PL005

Lublin, Poland, 20-109

PL013

Piekary Slaskie, Poland, 41-940

PL003

Skorzewo, Poland, 60-185

PL007

Starogard Gdanski, Poland, 83-200

PL012

Swicie n/Wisla, Poland, 86-100

PL009

Szczecin, Poland, 71-460

PL001

Torun, Poland, 87-100

Russian Federation

RU002

Leningrad, Russian Federation, 18861

RU013

Rostov on Don, Russian Federation, 344010

RU001

St. Petersburg, Russian Federation, 193015

RU003

St. Petersburg, Russian Federation, 197198

RU005

St. Petersburg, Russian Federation, 192019

RU006

St. Petersburg, Russian Federation, 192019

RU012

St. Petersburg, Russian Federation, 194022

RU004

Voronezh, Russian Federation, 394000

Slovakia

SK001

Banska Bysterica, Slovakia, 974 01

SK002

Krupina, Slovakia, 963 01

SK004

Nitra, Slovakia, 949 01

SK005

Rimavska Sobota, Slovakia, 97912

Ukraine

UA001

Chernihiv, Ukraine, 14000

UA008

Dnipropetrovsk, Ukraine, 49616

UA003

Donetsk, Ukraine, 83037

UA004
Glevakha, Ukraine, 8630
UA007
Kharkiv, Ukraine, 61068
UA009
Kherson, Ukraine, 73488
UA002
Kyiv, Ukraine, 4080
UA005
Odessa, Ukraine, 65006
UA006
Simferopol, Ukraine, 95006
UA010
Ternopil, Ukraine, 46020

United Kingdom

GB007
Birmingham, United Kingdom, B15 2SQ
GB006
Glasgow, United Kingdom
GB009
London, United Kingdom
GB008
Manchester, United Kingdom, M15 6SX
GB005
Reading, United Kingdom, RG2 0TG

Investigators

Study Director:	Email contact via H. Lundbeck A/S	LundbeckClinicalTrials@lundbeck.com

More Information

Responsible Party: H. Lundbeck A/S
Study ID Numbers: 12013A
2007-002315-92 [EudraCT Number]
Health Authority: Belgium: Federal Agency for Medicinal Products and Health Products
Czech Republic: State Institute for Drug Control
Estonia: The State Agency of Medicine
Hungary: National Institute of Pharmacy
Latvia: State Agency of Medicines
Lithuania: State Medicine Control Agency - Ministry of Health
Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Russia: Ministry of Health of the Russian Federation
Slovakia: State Institute for Drug Control
Ukraine: Ministry of Health
United Kingdom: Medicines and Healthcare Products Regulatory Agency

Study Results

Participant Flow

Recruitment Details	
Pre-Assignment Details	

Arm/Group Title	Placebo	Nalmefene 18.06 mg	Total (Not public)
Arm/Group Description	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks	
Period Title: **All Randomised Patients**			
Started	166	509	675
Completed	164	501	665
Not Completed	2	8	10
Reason Not Completed			
Did not receive placebo/nalmefene	2	8	10
(Not Public)	Not Completed = 2 Total from all reasons = 2	Not Completed = 8 Total from all reasons = 8	
Period Title: **All Treated Patients**			
Started	164	501	665
Completed	112 [1]	310 [2]	422
Not Completed	52	191	243
Reason Not Completed			
Adverse Event	2	43	45
Lack of Efficacy	2	3	5
Non-compliance	1	8	9
Protocol Violation	5	17	22
Withdrawal by Subject	35	94	129
Lost to Follow-up	3	12	15
Other Reason	4	14	18
(Not Public)	Not Completed = 52 Total from all reasons = 52	Not Completed = 191 Total from all reasons = 191	

[1] Patients who had the final visit of the study protocol

[2] Patients who had the final visit of the study protocol

Baseline Characteristics

Arm/Group Title ▼ Arm/Group Description	Placebo as-needed use, tablets, orally, 52 weeks	Nalmefene 18.06 mg as-needed use, tablets, orally, 52 weeks	Total
Overall Number of Baseline Participants	166	509	**675**
▼ Baseline Analysis Population Description [Not specified]			
Age, Continuous [1] Mean (Standard Deviation) Units: years	44.3 (12.0)	44.3 (11.2)	44.3 (11.4)
	[1] All-patients-randomised set (APRS).		
Gender, Male/Female [1] Measure Type: Number Units: participants NOTE : Baseline Measure Description is shorter than the Baseline Measure Title.			
Female	39	116	155
Male	127	393	520
	[1] APRS.		
Previously Treated for Alcohol Dependence [1] Measure Type: Number Units: participants NOTE : Baseline Measure Description is shorter than the Baseline Measure Title.			
NO	105	338	443
YES	61	171	232
	[1] APRS.		
Previously Treated for Alcohol Withdrawal Symptoms [1] Measure Type: Number Units: participants NOTE : Baseline Measure Description is shorter than the Baseline Measure Title.			
NO	118	372	490
YES	48	137	185

	[1] APRS.		
Total Monthly Heavy Drinking Days (HDD) **[1]** Mean (Standard Deviation) Units: days	13.69 (6.03)	14.08 (6.22)	13.98 (6.17)
	[1] APRS. Based on Timeline Followback (TLFB) data from the month preceding the screening visit.		
Total Alcohol Consumption (TAC) g Alcohol/Day **[1]** Mean (Standard Deviation) Units: g	68.00 (40.62)	68.64 (39.98)	68.49 (40.11)
	[1] APRS. Based on TLFB data from the month preceding the screening visit.		
Drinking Risk Level (DRL) **[1]** Measure Type: Number Units: participants NOTE : Baseline Measure Description is shorter than the Baseline Measure Title.			
UNKNOWN	0	1	1
LOW	26	79	105
MEDIUM	49	167	216
HIGH	59	148	207
VERY HIGH	32	114	146
	[1] APRS.		
Clinical Global Impression - Severity of Illness (CGI-S) **[1]** Mean (Standard Deviation) Units: units on a scale	3.88 (1.03)	3.95 (1.12)	3.94 (1.09)
	[1] APRS. The Clinical Global Impression - Severity of Illness (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).		
Gamma-glutamyl Transferase (GGT) **[1]** Mean (Standard Deviation) Units: international units per liter (IU/L) NOTE : Baseline Measure Description is shorter than the Baseline			69.36

Measure Title.	71.03 (116.25)	68.82 (109.87)	(111.39)
	[1] APRS.		
Alanine Aminotransferase (ALAT) **[1]** Mean (Standard Deviation) Units: IU/L NOTE : Baseline Measure Description is shorter than the Baseline Measure Title.	31.46 (20.20)	33.87 (22.61)	33.28 (22.05)
	[1] APRS.		

Outcome Measures

1. Primary Outcome

Title:	Number of Patients With Adverse Events (AEs)
Description:	Overview of AEs NOTE : Outcome Measure Description is shorter than the Outcome Measure Title.
Time Frame:	Serious Adverse Events: 52 weeks and a safety follow-up (visit/telephone call) scheduled for 4 weeks after completion of the study or after withdrawal from the study. Other Adverse Events: 52 weeks.
Safety Issue?	Yes

Outcome Measure Data

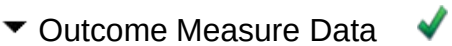
Analysis Population Description

All-patients-treated set (APTS) - all patients in the APRS excluding those with no recorded investigational medicinal product (IMP) intake and all IMP returned

Arm/Group Title	Placebo	Nalmefene 18.06 mg
Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	164	501
Measure Type: Number Units: participants		
Patients with AEs	103	377
Patients with Serious AEs (SAEs)	8	35
Patients with AEs Leading to Withdrawal	5	57

2. Primary Outcome

Title:	Percentage of Patients Who Withdrew Due to Intolerance to Treatment
▼ Description:	[Not specified]
Time Frame:	Baseline to Week 52
Safety Issue?	Yes

▼ Outcome Measure Data 

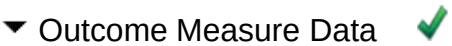
▼ Analysis Population Description

All-patients-treated Set (APTS)

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	164	501
Measure Type: Number Units: percentage of participants	1.2	8.6

3. Primary Outcome

Title:	Change From Baseline in the Monthly Number of Heavy Drinking Days (HDDs)
▼ Description:	Number of HDDs over a month (28 days), where one HDD was defined as a day with alcohol consumption ≥60 grams (g) for men and ≥40 g for women.
Time Frame:	Baseline and Month 6
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

Full-analysis set (FAS) - all patients in the APTS who had at least one valid post-baseline assessment in the main treatment period of both co-primary efficacy variables (HDD and TAC) and had an average alcohol consumption at medium Drinking Risk Level (DRL) or above according to WHO criteria at Baseline.

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants	110	320

Analyzed		
Mean (Standard Error) Units: days	-8.92 (0.56)	-9.80 (0.35)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	The primary hypothesis concerned the treatment effect at Month 6. Null hypothesis of no difference in treatment effect was tested against the alternative hypothesis that there was a difference in treatment effect. MMRM model with the Baseline score as a covariate; site, sex, time in months (Month 1-13); and treatment as fixed effects. The Baseline score-by-time and treatment-by-time interactions were also included in the model. An unstructured covariance matrix was used.

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.160
	Comments	[Not specified]
	Method	Other [Adjusted change from Baseline to Month 6]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.88
	Confidence Interval	(2-Sided) 95% -2.10 to 0.35
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.62
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 110 participants in the placebo group and 320 participants in the nalmefene group.

4. Primary Outcome

Title:	Change From Baseline in the Monthly Total Alcohol Consumption (TAC)
▼ Description:	TAC was defined as mean daily alcohol consumption in g/day over a month (28 days).
Time Frame:	Baseline and Month 6
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description
FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks

Number of Participants Analyzed	110	320
Mean (Standard Error) Units: g	-45.58 (2.61)	-49.05 (1.64)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	The primary hypothesis concerned the treatment effect at Month 6. The null hypothesis of no difference in treatment effect was tested against the alternative hypothesis that there was a difference in treatment effect. MMRM model with the Baseline score as a covariate; site, sex, time in months (Month 1-13); and treatment as fixed effects. The Baseline score-by-time and treatment-by-time interactions were also included in the model. An unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.232
	Comments	[Not specified]
	Method	Other [Adjusted change from Baseline to Month 6]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-3.47
	Confidence Interval	(2-Sided) 95% -9.17 to 2.23
	Parameter Dispersion	Type: Standard Error of the mean Value: 2.90
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 110 participants in the placebo group and 320 participants in the nalmefene group.

5. Secondary Outcome

Title:	Drinking Risk Level (RSDRL) Response
▼ Description:	RSDRL response was defined as a downward shift from baseline in Drinking Risk Level (DRL); 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.
Time Frame:	Month 6
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description
FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	137	415
Measure Type: Number Units: percentage of participants	63.5	62.2

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	The analysis of RSDRL used a logistic regression (LREG) model, with country, sex, Baseline DRL, and treatment as fixed effects, and missing values were imputed using individual-patient predicted values of TAC derived from the MMRM model.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.689
	Comments	[Not specified]
	Method	Other [Adjusted Odds Ratio (OR) response]

	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	0.92
	Confidence Interval	(2-Sided) 95% 0.59 to 1.41
	Estimation Comments	[Not specified]

6. Secondary Outcome

Title:	Change From Baseline in Clinical Status Using CGI-S
▼ Description:	The Clinical Global Impression - Severity of Illness (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).
Time Frame:	Baseline and Week 24
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	104	306
Mean (Standard Error) Units: units on a scale	-0.75 (0.08)	-0.94 (0.05)

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	MMRM model with the Baseline score as a covariate, and site, sex, time in weeks, and treatment as fixed effects. The Baseline score-by-time and treatment-by-time interactions were also included in the

		model; an unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.046
	Comments	[Not specified]
	Method	Other [Adjusted change from Baseline to Week 24]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.18
	Confidence Interval	(2-Sided) 95% -0.37 to -0.00
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.09
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 104 participants in the placebo group and 306 participants in the nalmefene group.

7. Secondary Outcome

Title:	Change in Clinical Status Using the CGI-I
▼ Description:	The Clinical Global Impression - Global Improvement (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).
Time Frame:	Week 24
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description
FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	104	306
Mean (Standard Error) Units: units on a scale	2.68 (0.10)	2.54 (0.06)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	MMRM model with the Baseline CGI-S score as a covariate, and site, sex, time in weeks, and treatment as fixed effects. The Baseline CGI-S score-by-time and treatment by- time interactions were also included in the model. An unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.217
	Comments	[Not specified]
	Method	Other [Adjusted change from Baseline to Week 24]

	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.14
	Confidence Interval	(2-Sided) 95% -0.36 to 0.08
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.11
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 104 participants in the placebo group and 306 participants in the nalmefene group.

8. Secondary Outcome

Title:	Liver Function Test Gamma-glutamyl Transferase (GGT)
▼ Description:	GGT values NOTE : Outcome Measure Description is shorter than the Outcome Measure Title.
Time Frame:	Week 24
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	108	319
Geometric Mean (Geometric Coefficient of Variation) Units: IU/L	34.5 (63.5%)	32.2 (71.1%)

▼ Statistical Analysis 1 ✔

Statistical Analysis	Comparison Groups	Placebo, Nalmefene 18.06 mg

Overview	Comments	Log-transformed GGT values were analysed using an MMRM model with the logtransformed Baseline value as a covariate, and site, sex, time in weeks, and treatment as fixed effects. Log-transformed Baseline value-by-time interaction and treatment-by-time interaction were included in the model. An unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.273
	Comments	[Not specified]
	Method	Other [Adjusted values]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Ratio to placebo]
	Estimated Value	0.93
	Confidence Interval	(2-Sided) 95% 0.83 to 1.05
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 108 participants in the placebo group and 319 participants in the nalmefene group.

9. Secondary Outcome

Title:	Liver Function Test Alanine Aminotransferase (ALAT)
▼ Description:	ALAT values NOTE : Outcome Measure Description is shorter than the Outcome Measure Title.
Time Frame:	Week 24
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	108	318
Geometric Mean (Geometric Coefficient of Variation) Units: IU/L	25.8 (52.4%)	25.6 (56.7%)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	Log-transformed ALAT values were analysed using an MMRM model with the logtransformed Baseline value as a covariate, and site, sex, time in weeks, and treatment as fixed effects. Log-transformed Baseline value-by-time and treatment-by-time interactions were included in the model. An unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.916
	Comments	[Not specified]

	Method	Other [Adjusted values]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Ratio to placebo]
	Estimated Value	0.99
	Confidence Interval	(2-Sided) 95% 0.90 to 1.10
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 108 participants in the placebo group and 318 participants in the nalmefene group.

10. Secondary Outcome

Title:	Change From Baseline in the Monthly Number of Heavy Drinking Days (HDDs)
▼ Description:	Number of HDDs over a month (28 days), where one HDD was defined as a day with alcohol consumption ≥60 g for men and ≥40 g for women.
Time Frame:	Baseline and Month 13
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	97	258
Mean (Standard Error) Units: days	-8.96 (0.58)	-10.53 (0.37)

▼ Statistical Analysis 1 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	MMRM model with the Baseline score as a covariate; site, sex,

		time in months (Month 1-13); and treatment as fixed effects. The Baseline score-by-time and treatment-by-time interactions were also included in the model. An unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.017
	Comments	[Not specified]
	Method	Other [Adjusted change from Baseline - Month 13]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.57
	Confidence Interval	(2-Sided) 95% -2.85 to -0.29
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.65
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 97 participants in the placebo group and 258 participants in the nalmefene group.

11. Secondary Outcome

Title:	Change From Baseline in the Monthly Total Alcohol Consumption (TAC)
▼ Description:	TAC was defined as mean daily alcohol consumption in g/day over a month (28 days).
Time Frame:	Baseline and Month 13
Safety Issue?	No

▼ Outcome Measure Data ✔

▼

Analysis Population Description
FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	97	258
Mean (Standard Error) Units: g	-46.33 (2.73)	-52.80 (1.76)

▼ Statistical Analysis 1 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	MMRM model with the Baseline score as a covariate; site, sex, time in months (Month 1-13); and treatment as fixed effects. The Baseline score-by-time and treatment-by-time interactions were also included in the model. An unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.036
	Comments	[Not specified]
	Method	Other [Adjusted change from Baseline - Month 13]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-6.47
	Confidence Interval	(2-Sided) 95% -12.53 to -0.42
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.07
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 97 participants in the placebo group and 258 participants in the nalmefene group.

12. Secondary Outcome

Title:	Drinking Risk Level (RSDRL) Response
▼ Description:	RSDRL response was defined as a downward shift from baseline in Drinking Risk Level (DRL); 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.
Time Frame:	Month 13
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description
FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	137	415
Measure Type: Number Units: percentage of participants	54.0	54.5

▼ Statistical Analysis 1 

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	The analysis of RSDRL used a logistic regression (LREG)

		model, with country, sex, Baseline DRL, and treatment as fixed effects, and missing values were imputed using individual-patient predicted values of TAC derived from the MMRM model.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.976
	Comments	[Not specified]
	Method	Other [Adjusted Odds Ratio (OR) response]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.01
	Confidence Interval	(2-Sided) 95% 0.67 to 1.52
	Estimation Comments	[Not specified]

13. Secondary Outcome

Title:	Change From Baseline in Clinical Status Using CGI-S
▼ Description:	The Clinical Global Impression - Severity of Illness (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).
Time Frame:	Baseline and Week 52
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description
FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg

▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	95	258
Mean (Standard Error) Units: units on a scale	-1.08 (0.10)	-1.30 (0.06)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	MMRM model with the Baseline score as a covariate, and site, sex, time in weeks, and treatment as fixed effects. The Baseline score-by-time and treatment-by-time interactions were also included in the model; an unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.056
	Comments	[Not specified]
	Method	Other [Adjusted change from

		Baseline to Week 52]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.22
	Confidence Interval	(2-Sided) 95% -0.44 to 0.01
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.11
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 95 participants in the placebo group and 258 participants in the nalmefene group.

14. Secondary Outcome

Title:	Change in Clinical Status Using the CGI-I
▼ Description:	The Clinical Global Impression - Global Improvement (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).
Time Frame:	Week 52
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	95	258
Mean (Standard Error) Units: units on a scale	2.52 (0.10)	2.26 (0.06)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	MMRM model with the Baseline CGI-S score as a covariate, and site, sex, time in weeks, and treatment as fixed effects. The Baseline CGI-S score-by-time and treatment by- time interactions were also included in the model. An unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.029
	Comments	[Not specified]
	Method	Other [Adjusted change from Baseline to Week 52]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.26
	Confidence Interval	(2-Sided) 95% -0.50 to -0.03
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.12
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 95 participants in the placebo group and 258 participants in the nalmefene group.

15. Secondary Outcome

Title:	Liver Function Test Gamma-glutamyl Transferase (GGT)
▼ Description:	GGT values NOTE : Outcome Measure Description is shorter than the Outcome Measure Title.
Time Frame:	Week 52

Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	98	259
Geometric Mean (Geometric Coefficient of Variation) Units: IU/L	41.3 (76.2%)	32.0 (80.6%)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	Log-transformed GGT values were analysed using an MMRM model with the logtransformed Baseline value as a covariate, and site, sex, time in weeks, and treatment as fixed effects. Log-transformed Baseline value-by-time interaction and treatment-by-time interaction were included in the model. An unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.001
	Comments	[Not specified]

	Method	Other [Adjusted values]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Ratio to placebo]
	Estimated Value	0.78
	Confidence Interval	(2-Sided) 95% 0.67 to 0.90
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 98 participants in the placebo group and 259 participants in the nalmefene group.

16. Secondary Outcome

Title:	Liver Function Test Alanine Aminotransferase (ALAT)
▼ Description:	ALAT values NOTE : Outcome Measure Description is shorter than the Outcome Measure Title.
Time Frame:	Week 52
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

FAS

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description:	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks
Number of Participants Analyzed	97	259
Geometric Mean (Geometric Coefficient of Variation) Units: IU/L	27.8 (55.6%)	24.6 (58.5%)

▼ Statistical Analysis 1 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Nalmefene 18.06 mg
	Comments	Log-transformed GGT values

		were analysed using an MMRM model with the logtransformed Baseline value as a covariate, and site, sex, time in weeks, and treatment as fixed effects. Log-transformed Baseline value-by-time interaction and treatment-by-time interaction were included in the model. An unstructured covariance matrix was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.037
	Comments	[Not specified]
	Method	Other [Adjusted values]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Ratio to placebo]
	Estimated Value	0.88
	Confidence Interval	(2-Sided) 95% 0.79 to 0.99
	Estimation Comments	The Number of Participants Analyzed is participants with efficacy measurement available at this endpoint, that is, 97 participants in the placebo group and 259 participants in the nalmefene group.

Adverse Events

Time Frame	Serious Adverse Events: 52 weeks and a safety follow-up (visit/telephone call) scheduled for 4 weeks after completion of the study or after withdrawal from the study. Other Adverse Events: 52 weeks.
Additional Description	
Source Vocabulary Name	[Not specified]
Assessment Type	[Not specified]

	NOTE : An Assessment Type for Table Default has not been specified.

Arm/Group Title	Placebo	Nalmefene 18.06 mg
▼ Arm/Group Description	as-needed use, tablets, orally, 52 weeks	as-needed use, tablets, orally, 52 weeks

▼ Serious Adverse Events

	Placebo	Nalmefene 18.06 mg
	Affected / at Risk (%)	Affected / at Risk (%)
Total	8/164 (4.88%)	35/501 (6.99%)
Cardiac disorders		
Atrial fibrillation [A]	0/164 (0%)	2/501 (0.4%)
Ventricular extrasystoles [A]	0/164 (0%)	1/501 (0.2%)
Congenital, familial and genetic disorders		
Adenomatous polyposis coli [A]	0/164 (0%)	1/501 (0.2%)
Eye disorders		
Diplopia [A]	0/164 (0%)	1/501 (0.2%)
Gastrointestinal disorders		
Crohn's disease [A]	1/164 (0.61%)	0/501 (0%)
Diverticulum intestinal [A]	1/164 (0.61%)	0/501 (0%)
Large intestine perforation [A]	0/164 (0%)	1/501 (0.2%)
Oesophagitis ulcerative [A]	0/164 (0%)	1/501 (0.2%)
General disorders		
Non-cardiac chest pain [A]	0/164 (0%)	1/501 (0.2%)
Hepatobiliary disorders		
Liver disorder [A]	1/164 (0.61%)	0/501 (0%)
Infections and infestations		
Abscess limb [A]	1/164 (0.61%)	0/501 (0%)
Bronchopneumonia [A]	0/164 (0%)	1/501 (0.2%)
Pneumonia [A]	1/164 (0.61%)	1/501 (0.2%)
Pulmonary tuberculosis [A]	0/164 (0%)	1/501 (0.2%)
Pyelonephritis [A]	1/164 (0.61%)	0/501 (0%)
Pyothorax [A]	1/164 (0.61%)	0/501 (0%)
Injury, poisoning and procedural complications		
Alcohol poisoning [A]	0/164 (0%)	1/501 (0.2%)
Fall [A]	0/164 (0%)	2/501 (0.4%)
Fibula fracture [A]	1/164 (0.61%)	0/501 (0%)

Ligament rupture	A	0/164 (0%)	1/501 (0.2%)
Rib fracture	A	1/164 (0.61%)	0/501 (0%)
Tibia fracture	A	1/164 (0.61%)	0/501 (0%)
Traumatic brain injury	A	0/164 (0%)	1/501 (0.2%)
Ulna fracture	A	0/164 (0%)	1/501 (0.2%)
Upper limb fracture	A	0/164 (0%)	1/501 (0.2%)
Metabolism and nutrition disorders			
Decreased appetite	A	0/164 (0%)	1/501 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal carcinoma	A	0/164 (0%)	1/501 (0.2%)
Prostate cancer	A	0/164 (0%)	1/501 (0.2%)
Nervous system disorders			
Balance disorder	A	0/164 (0%)	1/501 (0.2%)
Epilepsy	A	0/164 (0%)	1/501 (0.2%)
Headache	A	0/164 (0%)	1/501 (0.2%)
Syncope	A	0/164 (0%)	1/501 (0.2%)
Psychiatric disorders			
Alcohol abuse	A	1/164 (0.61%)	1/501 (0.2%)
Alcohol withdrawal syndrome	A	1/164 (0.61%)	9/501 (1.8%)
Alcoholic hangover	A	0/164 (0%)	1/501 (0.2%)
Alcoholism	A	0/164 (0%)	1/501 (0.2%)
Anorexia nervosa	A	0/164 (0%)	1/501 (0.2%)
Anxiety	A	0/164 (0%)	1/501 (0.2%)
Depression	A	0/164 (0%)	1/501 (0.2%)
Disorientation	A	0/164 (0%)	2/501 (0.4%)
Insomnia	A	0/164 (0%)	1/501 (0.2%)
Nightmare	A	0/164 (0%)	1/501 (0.2%)
Suicidal behaviour	A	0/164 (0%)	1/501 (0.2%)
Respiratory, thoracic and mediastinal disorders			
Pneumothorax	A	1/164 (0.61%)	0/501 (0%)
Vascular disorders			
Arteritis	A	0/164 (0%)	1/501 (0.2%)
Hypertension	A	1/164 (0.61%)	0/501 (0%)

Indicates events were collected by non-systematic methods.

A Term from vocabulary, Meddra 13.0

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events		5%	
		Placebo	**Nalmefene 18.06 mg**
		Affected / at Risk (%)	Affected / at Risk (%)
Total		57/164 (34.76%)	273/501 (54.49%)
Gastrointestinal disorders			
Nausea	A	9/164 (5.49%)	112/501 (22.36%)
Vomiting	A	2/164 (1.22%)	57/501 (11.38%)
General disorders			
Fatigue	A	3/164 (1.83%)	27/501 (5.39%)
Infections and infestations			
Nasopharyngitis	A	19/164 (11.59%)	54/501 (10.78%)
Injury, poisoning and procedural complications			
Accidental overdose	A	9/164 (5.49%)	9/501 (1.8%)
Fall	A	11/164 (6.71%)	5/501 (1%)
Nervous system disorders			
Dizziness	A	6/164 (3.66%)	73/501 (14.57%)
Headache	A	13/164 (7.93%)	61/501 (12.18%)
Somnolence	A	8/164 (4.88%)	42/501 (8.38%)
Psychiatric disorders			
Insomnia	A	11/164 (6.71%)	73/501 (14.57%)

Indicates events were collected by non-systematic methods.

A Term from vocabulary, Meddra 13.0

Limitations and Caveats

[Not Specified]

More Information

Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The main publication has to be published before any sub publication. The investigators shall obtain Lundbeck's written approval before publishing any publication relating to nalmefene, the Study, the Protocol and/or the results recorded during the Study.

Results Point of Contact

Name/Official	H. Lundbeck A/S
Title:	
Organization:	H. Lundbeck A/S
Phone:	+45 3630 1311
Email:	LundbeckClinicalTrials@lundbeck.com

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