Clinical trial results:
Double-blind, placebo-controlled randomised study on the efficacy of naloxone nasal spray for the treatment of gambling disorder

Summary

EudraCT number	2017-001946-93
Trial protocol	FI
Global end of trial date	16 October 2019

Results information

Result version number	v1 (current)
This version publication date	28 May 2022
First version publication date	28 May 2022
Summary attachment (see zip file)	NalGamb synopsis (Alho et al NalGamb Synopsis_ EudraCT.docx)

Trial information

Trial identification

Sponsor protocol code	NalGamb

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03430180
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Finnish Institute for Health and Welfare
Sponsor organisation address	PL 30, Mannerheimintie 166, Helsinki, Finland, 00271
Public contact	Clinical Trial Information, Finnish Institute of Health and Welfare, 358 9295248124, sari.castren@thl.fi
Scientific contact	Clinical Trial Information, Finnish Institute of Health and Welfare, 0295248525 9295248124, sari.castren@thl.fi

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	20 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2019
Global end of trial reached?	Yes
Global end of trial date	16 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether treatment with naloxone hydrochloride nasal spray reduces gambling urge symptoms in patients with gambling disorder.

Protection of trial subjects:

Adverse events were monitored daily via e-diary, when detected, participants were contacted, advised and referred, if needed, to appropriate care.
Well being of the participants were carefully monitored and assessed in all contact points screening, bl, week 3, week 6, week 9 and week 12 appointments with highly trained clinical team and follow up call was taken place at week 14.

Background therapy:

All participants received psychosocial support regardless of the treatment group.

Evidence for comparator: -

Actual start date of recruitment	30 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 126
Worldwide total number of subjects	126
EEA total number of subjects	126

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)	126
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited through advertising online and in newspapers directing them to the study website where potential study participants completed the South Oaks Gambling Screen-Revised (SOGS-R; Abbott & Volberg, 1996) test as an online pre-screening assessment.

Pre-assignment

Screening details:

2.4.1. Screening
Clinic visit: Informed consent was obtained. After initial screening assessments, eligible participants repeated the SOGS-R test and were assessed for gambling craving (G-SAS, VAS), gambling severity (PGSI, NODS, DSM-5), internet use (IDS9-SF), QoL (EUROHIS-8) alcohol con- sumption (AUDIT), smoking and depression (MADRS) and clini

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The study was double-blinded, so neither the investigator nor subject knew the treatment to which a particular group the subject had been randomised.
The randomisation , labelling and packaging of IMP were undertaken nu an independent contractor and so investigator, data management and statistics personel were blinded to treatment allocation. IMP for both treatment groups were provided in identical nasal sprays. Permuted block randomisation sequence (1:1 ratio 2 treatment arms).

Arms

Are arms mutually exclusive?	Yes
Arm title	Naloxone

Arm description:

Participants were randomised on a 1:1 basis to receive either the naloxone hydrochloride nasal spray or a matching placebo spray.

Arm type	Active comparator
Investigational medicinal product name	Naloxone hydrocholoride nasal spay
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Intranasal use

Dosage and administration details:

Participants were instructed to administer the investigational me- dicinal product (IMP) nasally, 1 spray (0.1 mL 4 mg) into 1 nostril up to 4 times per day (maximum daily dose: 16 mg) as needed in response to a gambling urge or when the likelihood of gambling was considered high, for 12 weeks.

Arm title	Plasebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Plasebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

Participants were instructed to administer the investigational medicinal product (IMP) nasally, 1 spray (0.1 mL = 4 mg) into 1 nostril up to 4 times per day (maximum daily dose: 16 mg) as needed in response to a gambling urge or when the likelihood of gambling was considered high, for 12 weeks.

Number of subjects in period 1	Naloxone	Plasebo
Started	62	64
Completed	62	52
Not completed	0	12
Consent withdrawn by subject	-	12

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	126	126	
Age categorical			
Age males: Naloxone group (n=¼ 62) 41.40 ± 13.52 Plasebo group (n= ¼64) 43.09 ± 16.99 Age females: Naloxone group 50.82 ± 15.93 Placebo group 49.62 ± 14.18			
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
from 18-75	126	126	
Gender categorical			
Approximately 70% (n = 88) of the subjects were males.			
Units: Subjects			
Female	38	38	
Male	88	88	

Subject analysis sets

Subject analysis set title	demographic and baseline characteristics
Subject analysis set type	Per protocol

Subject analysis set description:

The participants were on average 45 years old (within the group's overall age range of 18 to 75 years). Approximately 70% (n 88) of the subjects were males. The majority of participants were Caucasians (n 125, 99%). There were no notable differences in demographics between the treatment groups (Table 3).
Sixty-eight participants (54%) were married or cohabiting. Most participants lived either alone (n 52, 41%) or with their family (n 71, 56%). Participants were mainly employed as office workers or clerks (n 69, 55%), and 30 participants (24%) had retired. Almost all par- ticipants (n 115, n 91%) reported that they currently consumed alcohol and 56 participants (44%) were current smokers. The proportion of current smokers was higher in the IN naloxone group (55%) as compared to the placebo group (34%).
No participant was excluded due the risk of suicide or suicidal ideation (C-SSRS). Both groups were on average equally ready and motivated for change as measured on a 10 cm VAS scal

Reporting group values	demographic and baseline characteristics		
Number of subjects	126		
Age categorical			
Age males: Naloxone group (n=¼ 62) 41.40 ± 13.52 Plasebo group (n= ¼64) 43.09 ± 16.99 Age females: Naloxone group 50.82 ± 15.93 Placebo group 49.62 ± 14.18			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
from 18-75	126		
Gender categorical			
Approximately 70% (n = 88) of the subjects were males.			
Units: Subjects			
Female	38		
Male	88		

End points

End points reporting groups

Reporting group title	Naloxone

Reporting group description:

Participants were randomised on a 1:1 basis to receive either the naloxone hydrochloride nasal spray or a matching placebo spray.

Reporting group title	Plasebo

Reporting group description: -

Subject analysis set title	demographic and baseline characteristics
Subject analysis set type	Per protocol

Subject analysis set description:

The participants were on average 45 years old (within the group's overall age range of 18 to 75 years). Approximately 70% (n 88) of the subjects were males. The majority of participants were Caucasians (n 125, 99%). There were no notable differences in demographics between the treatment groups (Table 3).
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No participant was excluded due the risk of suicide or suicidal ideation (C-SSRS). Both groups were on average equally ready and motivated for change as measured on a 10 cm VAS scal

Primary: G-SAS, Gambling Assessment Scale

End point title	G-SAS, Gambling Assessment Scale

End point description:

The Gambling Assessment Scale (G-SAS; Kim et al., 2001; Kim et al., 2009).

End point type	Primary

End point timeframe:

From baseline to week 12

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: 5-point scale from 0-4 total score 48	62	64		

Attachments (see zip file)	A scatterplot of G-SAS total score values from Bas/EudraCT_G-

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

The primary endpoint G-SAS total score was modelled by the linear mixed-effects model. The effect of treatment and time factors were tested by the likelihood ratio test. Similarly, the linear mixed-effects model analysis was performed for total scores of second endpoint vari- ables. Each separate G-SAS variable was also modelled by the proportional-odds cumulative logit mixed model with use of the

ordinal package in R software 4.0.5. Multivariate repeated measures analysis for G-SAS variables

Comparison groups	Naloxone v Plasebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[1] - he primary endpoint G-SAS total score was modelled by the linear mixed-effects model. The effect of treatment and time factors were tested by the likelihood ratio test. Similarly, the linear mixed-effects model analysis was performed for total scores of second endpoint variables. Each separate G-SAS variable was also modelled by the proportional-odds cumulative logit mixed model with use of the ordinal package in R software 4.0.5. Multivariate repeated measures analysis for G-SAS variab

Secondary: VAS (craving)

End point title	VAS (craving)

End point description:

Visual analogue scale (VAS) (gambling craving) from Baseline to Week 3, 6, 9 and 12.

End point type	Secondary

End point timeframe:

Visual analogue scale (VAS) (gambling craving) from Baseline to Week 3, 6, 9 and 12.

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: 0-10	62	64		

Statistical analyses

No statistical analyses for this end point

Secondary: PGSI

End point title	PGSI

End point description:

Gambling severity (Problem Gambling Severity Index [PGSI]) from Baseline to Week 6 and 12

End point type	Secondary

End point timeframe:

Gambling severity (Problem Gambling Severity Index [PGSI]) from Baseline to Week 6 and 12

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: 0-8	62	64		

Attachments (see zip file)	A scatterplot of PGSI total score values from Base/EudraCT

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

The primary endpoint G-SAS total score was modelled by the linear mixed-effects model. The effect of treatment and time factors were tested by the likelihood ratio test. Similarly, the linear mixed-effects model analysis was performed for total scores of second endpoint vari- ables. Each separate G-SAS variable was also modelled by the proportional-odds cumulative logit mixed model with use of the ordinal package in R software 4.0.5. Multivariate repeated measures analysis for G-SAS variables wa

Comparison groups	Naloxone v Plasebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.01
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Secondary: DSM-5

End point title	DSM-5

End point description:

Gambling severity (Diagnostic and Statistical Manual for Mental Disorders, 5th edition [DSM-5]) from Baseline to Week 6 and 12

End point type	Secondary

End point timeframe:

Gambling severity (Diagnostic and Statistical Manual for Mental Disorders, 5th edition [DSM-5]) from Baseline to Week 6 and 12

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: 0-9	62	64		

Statistical analyses

No statistical analyses for this end point

Secondary: NODS

End point title	NODS

End point description:

Gambling problems (National Opinion Research Centre DSM Screen for Gambling Problems [NODS]) from Baseline to Week 3, 6, 9 and 12

End point type	Secondary

End point timeframe:

Gambling problems (National Opinion Research Centre DSM Screen for Gambling Problems [NODS]) from Baseline to Week 3, 6, 9 and 12

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: 0-10	62	64		

Statistical analyses

No statistical analyses for this end point

Secondary: Gambling expenditure

End point title	Gambling expenditure

End point description:

Gambling expenditure and frequency from Baseline to Week 12 (eDiary)

End point type	Secondary

End point timeframe:

Gambling expenditure and frequency from Baseline to Week 12 (eDiary)

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: euros				
number (not applicable)	62	64		

Attachments (see zip file)	A scatterplot of natural logarithm values of gambl/EudraCT -

Statistical analyses

No statistical analyses for this end point

Secondary: GASS

End point title	GASS

End point description:

Abstinence of gambling (Gambling Abstinence Self-Efficacy Scale [GASS]) from Baseline to Week 3, 6, 9 and 12.

End point type	Secondary

End point timeframe:

Abstinence of gambling (Gambling Abstinence Self-Efficacy Scale [GASS]) from Baseline to Week 3, 6, 9 and 12.

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: 0-5	62	64		

Statistical analyses

No statistical analyses for this end point

Secondary: IDS-9SF

End point title	IDS-9SF

End point description:

Internet use (Internet Disorder Scale-9 Short Form [IDS-9 SF]) from Baseline to Week 6 and 12.

End point type	Secondary

End point timeframe:

Internet use (Internet Disorder Scale-9 Short Form [IDS-9 SF]) from Baseline to Week 6 and 12.

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: 9-45	62	64		

Attachments (see zip file)	A scatterplot of IDS total score values from

Statistical analyses

No statistical analyses for this end point

Secondary: QoL

End point title	QoL

End point description:

QoL (World Health Organization European Health Interview Survey for QoL [WHO: EUROHIS-8]) from Baseline to Week 6 and 12.

End point type	Secondary

End point timeframe:

QoL (World Health Organization European Health Interview Survey for QoL [WHO: EUROHIS-8]) from Baseline to Week 6 and 12.

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: 1-5	62	64		

Attachments (see zip file)	A scatterplot of Quality of Life total score valu/EudraCT QoL.

Statistical analyses

No statistical analyses for this end point

Secondary: AUDIT

End point title	AUDIT

End point description:

Alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT]) from Baseline to Week 6 and 12

End point type	Secondary

End point timeframe:

Alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT]) from Baseline to Week 6 and 12

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: 0-20	62	64		

Attachments (see zip file)	A scatterplot of AUDIT total score values from /EudraCt

Statistical analyses

No statistical analyses for this end point

Secondary: smoking

End point title	smoking
End point description: Smoking from Screening to Week 12	
End point type	Secondary
End point timeframe: Smoking from Screening to Week 12	

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: units				
number (not applicable)	62	64		

Statistical analyses

No statistical analyses for this end point

Secondary: Madrs

End point title	Madrs
End point description: Depression (Montgomery-Asberg Depression Rating Scale [MADRS]) from Baseline to Week 6 and 12	
End point type	Secondary
End point timeframe: Depression (Montgomery-Asberg Depression Rating Scale [MADRS]) from Baseline to Week 6 and 12	

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: 0-6	62	64		

Attachments (see zip file)	A scatterplot of MADRS total score values from

Statistical analyses

No statistical analyses for this end point

Secondary: safety end points

End point title	safety end points

End point description:

Number and proportion of subjects with adverse events (AEs) Assessment of clinical laboratory parameters from Baseline to Week 12 Assessment of vital signs from Baseline to Week 6 and 12 Assessment of physical examination from Baseline to Week 12 Assessment of body weight from Baseline to Week 12
Assessment of examination of nasal mucosa from Baseline to Week 6 and Assessment of smell test from Baseline to Week 12

End point type	Secondary

End point timeframe:

Number and proportion of subjects with adverse events (AEs) Assessment of clinical laboratory parameters from Baseline to Week 12 Assessment of vital signs from Baseline to Week 6 and 12 Assessment of physical examination from Baseline to Week 12 Assessm

End point values	Naloxone	Plasebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	64		
Units: diary				
number (not applicable)	62	64		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

diary was used to gather any adverse events - diary was followed daily basis.

Adverse event reporting additional description:

The study eDiary was used to record changes in participant health status and was reviewed via each participant’s eDiary during their visit. The severity of each adverse event (AE) was to be characterised and then classified into 1 of the following 3 categories by the Investigator: Mild: The AE did not interfere in a significant manner with the subj

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	Naloxone

Reporting group description: -

Serious adverse events	Naloxone		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Naloxone		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 62 (82.26%)		
Product issues			
Headache			
subjects affected / exposed	51 / 62 (82.26%)		
occurrences (all)	51		

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