Clinical trial results:
Investigation of dose response relationships when using low dose naltrexone (LDN) for the treatment of fibromyalgia

Summary

EudraCT number	2016-002081-31
Trial protocol	DK
Global end of trial date	10 September 2018

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	16008

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Odense University Hospital
Sponsor organisation address	Sdr. Boulevard, Odense C, Denmark, 5000
Public contact	Karin Plesner, Anæstesiologisk-intensiv afd V, Odense Universitets Hospital, karin.bruun.plesner@rsyd.dk
Scientific contact	Karin Plesner, Anæstesiologisk-intensiv afd V, Odense Universitets Hospital, karin.bruun.plesner@rsyd.dk

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	31 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2018
Global end of trial reached?	Yes
Global end of trial date	10 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test different doses of low dosis naltrexone (LDN) in patients with fibromyalgia and to estimate effective dose in 50% and 95% of cases.

Protection of trial subjects:

No specific measures

Background therapy:

Subjects were allowed to continue their usual pain medication.
Opioids was not allowed during the trial and 8 weeks before inclusion.

Evidence for comparator: -

Actual start date of recruitment	28 December 2016
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	Denmark: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	54
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited in 2 periods:
Pre-period: December 12th 2016 to April 26th 2017. (8 subjects included)
Trial was interrupted and an amendment was made to the protocol. Study was restarted.
Period 1: June 7th 2017 to September 10th 2018. (27 subjects included)

Pre-assignment

Screening details:

Period 1: 28 subjects screened, 27 subjects included.

Pre-assignment period milestones

Number of subjects started	56[1]
Number of subjects completed	54

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: This i a study with 1 arm only.
Currently the system cannot accommodate this specific scenario. Hence we had to workaround this by adding a baseline arm that is considered one group and the end data another group. An equal number of subjects were added to the arms, giving a deviation in number of enrolled subjects.
This is done to be able to use the statistical analysis set to report analysis for a single arm.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline

Arm description:

Baseline

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Treatment LDN

Arm description:

LDN

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

Dosage and administration details:

One daily dosage in the evening.
Doses between 0,75 mg and 6 mg.

Number of subjects in period 1	Baseline	Treatment LDN
Started	27	27
Completed	25	25
Not completed	2	2
Consent withdrawn by subject	2	2

Baseline characteristics

Reporting groups

Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	54	54	
Age categorical 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	
Age continuous Units: years			
median	47		
full range (min-max)	27 to 59	-	
Gender categorical Units: Subjects			
Female	54	54	
Male	0	0	

End points

End points reporting groups	
Reporting group title	Baseline
Reporting group description:	
Baseline	
Reporting group title	Treatment LDN
Reporting group description:	
LDN	

Primary: Effective dose in 50%	
End point title	Effective dose in 50%
End point description:	
The end point is estimated based on the effect of different doses in the 25 subjects who completed the treatment period of 3 weeks, calculated based on the Up-and-down method.	
End point type	Primary
End point timeframe:	
From restart of the study after amendment to the protocol was made: From June 7th 2017 to September 10th 2018	

End point values	Baseline	Treatment LDN		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: 3.88				
arithmetic mean (confidence interval 95%)	3.88 (3.39 to 4.35)	3.88 (3.39 to 4.35)		

Statistical analyses

Statistical analysis title	Up-and-Down method
Comparison groups	Baseline v Treatment LDN
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other[1]
Method	Up-and-down method
Parameter estimate	PAVA estimate
Point estimate	3.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.39
upper limit	4.35
Variability estimate	Standard deviation

Notes:

[1] - Up-and-down method

Primary: Effective dose in 95 %

End point title	Effective dose in 95 %

End point description:

The end point is estimated based on the effect of different doses in the 25 subjects who completed the treatment period of 3 weeks, calculated based on the Up-and-down method.

End point type	Primary

End point timeframe:

From restart of the study after amendment to the protocol was made: From June 7th 2017 to September 10th 2018

End point values	Baseline	Treatment LDN		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: 5.40				
arithmetic mean (confidence interval 95%)	5.4 (4.66 to 6.13)	5.4 (4.66 to 6.13)		

Statistical analyses

Statistical analysis title	Up-and-Down method
Comparison groups	Baseline v Treatment LDN
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	PAVA estimate
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.66
upper limit	6.13
Variability estimate	Standard deviation

Notes:

[2] - Up-and-down method

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events reported at: Baseline, 2 weeks, 4 weeks.	
Adverse event reporting additional description:	
Regular interviews. Questionnaire about symptoms.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	V22.1

Reporting groups	
Reporting group title	Overall group
Reporting group description: -	

Serious adverse events	Overall group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (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	Overall group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 27 (92.59%)		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
Dizziness			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		

Sleep deficit	Additional description: Vivid dreams or restlessness during sleep		
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Increased appetite			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Psychiatric disorders			
Mood altered			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2017	Change of primary endpoint. Positive effect of treatment assessed by Patient Global Impression of Improvement on a 7-point Likert scale with the ancors: Very much worse, worse, little worse, no change, little better, better, very much better. Positive effect if: Little better, better, very much better.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 April 2017	Study interrupted because the chosen primary outcome fails to identify the subjects who reports a clinical relevant positive effect of the treatment.	07 June 2017

Notes:

Limitations and caveats

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

Given the sequential method we had to evaluate effect of the treatment after a relatively short period of time, and 2 weeks was chosen based on time-response curves from previous trials.

Notes: