Clinical trial results:
Fibromyalgia and Naltrexone: The FINAL study

Summary

EudraCT number	2019-000702-30
Trial protocol	DK
Global end of trial date	27 December 2022

Results information

Result version number	v1 (current)
This version publication date	07 January 2024
First version publication date	07 January 2024
Summary attachment (see zip file)	Journal article (Bruun2023_LDN 6 mg versus placebo_TheLancetRheum.pdf)

Trial information

Trial identification

Sponsor protocol code	18.021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04270877
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Odense University Hospital
Sponsor organisation address	J B Winsloewsvej 4, Odense C, Denmark, 5000
Public contact	Pain centre desk, Pain Centre Department of Anesthesiology, 0045 65413869, karin.due.bruun@rsyd.dk
Scientific contact	Chief physician Karin Due Bruun, Pain Centre Department of Anesthesiology, 0045 26183619, karin.due.bruun@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	05 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 December 2022
Global end of trial reached?	Yes
Global end of trial date	27 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the trial is to investigate whether treatment with Low dose Naltrexone (LDN) has a superior effect compared with placebo on pain in female patients with fibromyalgia, evaluated after 12 weeks of treatment.

Protection of trial subjects:

In several clinical studies LDN has been shown to be well tolerated when used for treatment of FM, MS or Crohns disease. No serious adverse events have been reported in any of the clinical studies of LDN. Participants will be titrated up to 6 mg following a dose escalation scheme: Initial dosage of 1.5 mg daily, escalated every seventh day by 1.5 mg up to 6 mg at week 4. Dose escalation will be based on safety and tolerability, and if dose escalation is not feasible, delayed increments are allowed. After end of titration (week 4) the subjects will be maintained at 6 mg or the highest tolerated dose level for the last 8 weeks of the treatment period.
AE and AR are registered at baseline (week 0) after 2, 4, 8 and 12 weeks of treatment and at the end of follow-up (week 16).
The participants will be withdrawn from the study in case of:
- Serious adverse reactions
- If the subject wants to withdraw

The participants are covered by the governmental patient insurance, which includes all patients in the Danish health care system.

Background therapy:

Participants continued their usual care.

Evidence for comparator:

No active comparator. It was a placebo controlled trial.

Actual start date of recruitment	04 January 2021
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	Denmark: 99
Worldwide total number of subjects	99
EEA total number of subjects	99

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)	99
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from the study site and through advertisements in national patient association magazines (both printed and internet-based).

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	99
Number of subjects completed	99

Period 1

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

Blinding implementation details:

A data manager, with no clinical involvement in the trial, prepares the randomization sequence. The allocation is concealed in a password-protected computer file that is only accessible by the data manager. The randomization list is sent to the hospital pharmacy, who labels the medicine with blinding codes according to this list. The medicine is then shipped to the place of the trial. Un-blinding will not take place before primary analysis of the data has taken place.

Arms

Are arms mutually exclusive?	Yes
Arm title	Naltrexone

Arm description:

Active treatment
Naltrexone 6 mg once daily for 12 weeks

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

Dosage and administration details:

6 mg once daily for 12 weeks

Arm title	Placebo

Arm description:

Placebo treatment
6 mg once daily for 12 weeks

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

Dosage and administration details:
6 mg once daily for 12 weeks

Number of subjects in period 1	Naltrexone	Placebo
Started	49	50
Completed	49	50

Baseline characteristics

Reporting groups	
Reporting group title	Naltrexone
Reporting group description:	
Active treatment Naltrexone 6 mg once daily for 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment 6 mg once daily for 12 weeks	

Reporting group values	Naltrexone	Placebo	Total
Number of subjects	49	50	99
Age categorical Units: Subjects			
Adults (18-64 years)	49	50	99
Age continuous Units: years			
median	50.8	50.4	
standard deviation	± 8.8	± 8.9	-
Gender categorical Units: Subjects			
Female	49	50	99
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Intention-to-treat analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
To test the efficcacy	

Reporting group values	Intention-to-treat analysis		
Number of subjects	99		
Age categorical Units: Subjects			
Adults (18-64 years)			
Age continuous Units: years			
median			
standard deviation	±		
Gender categorical Units: Subjects			
Female	99		
Male	0		

End points

End points reporting groups

Reporting group title	Naltrexone
Reporting group description:	
Active treatment Naltrexone 6 mg once daily for 12 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment 6 mg once daily for 12 weeks	
Subject analysis set title	Intention-to-treat analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
To test the efficcacy	

Primary: Average pain 7 days

End point title	Average pain 7 days
End point description:	
End point type	Primary
End point timeframe:	
12 week	

End point values	Naltrexone	Placebo	Intention-to-treat analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	50	99	
Units: 0-10 NRS				
least squares mean (confidence interval 95%)	-1.3 (-1.7 to -0.8)	-0.9 (-1.4 to -0.5)	-0.34 (-0.95 to -0.27)	

Statistical analyses

Statistical analysis title	Difference between groups
Statistical analysis description:	
Repeated measures mixed effects model	
Comparison groups	Naltrexone v Placebo v Intention-to-treat analysis
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	0.27
Variability estimate	Standard deviation
Dispersion value	1.5

Secondary: FIQR total score

End point title	FIQR total score

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: 0-100				
least squares mean (confidence interval 95%)	-2.50 (-6.73 to 1.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: WPI index

End point title	WPI index

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: 0-19				
least squares mean (confidence interval 95%)	-0.64 (-1.95 to 0.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tenderness

End point title	Tenderness

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: 0-10 NRS				
least squares mean (confidence interval 95%)	-0.24 (-0.92 to 0.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pressure pain treshhold

End point title	Pressure pain treshhold

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: Kilo Pascal				
least squares mean (confidence interval 95%)	11.70 (-9.41 to 32.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fatigue

End point title	Fatigue

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: 0-10 NRS				
least squares mean (confidence interval 95%)	-0.04 (-0.69 to 0.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sleep disturbance

End point title	Sleep disturbance

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: 0-10 NRS				
least squares mean (confidence interval 95%)	-0.16 (-0.99 to 0.68)			

Statistical analyses

No statistical analyses for this end point

Secondary: Depression

End point title	Depression

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: 0-10 NRS				
least squares mean (confidence interval 95%)	-0.18 (-0.86 to 0.50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anxiety

End point title	Anxiety

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: 0-10 NRS				
least squares mean (confidence interval 95%)	0.18 (-0.32 to 0.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Memory problems

End point title	Memory problems

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: 0-10 NRS				
least squares mean (confidence interval 95%)	-0.93 (-1.57 to -0.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Stiffness

End point title	Stiffness

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: 0-10 NRS				
least squares mean (confidence interval 95%)	-0.13 (-0.76 to 0.51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Physical function

End point title	Physical function

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: 0-90 NRS				
least squares mean (confidence interval 95%)	-1.63 (-6.33 to 3.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health related quality of life

End point title	Health related quality of life

End point description:

End point type	Secondary

End point timeframe:

12 week

End point values	Intention-to-treat analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: 0-100 VAS				
least squares mean (confidence interval 95%)	1.33 (-4.89 to 7.55)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 15% pain responder

End point title	15% pain responder
End point description: Supportive outcome	
End point type	Other pre-specified
End point timeframe: 12 week	

End point values	Naltrexone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	50		
Units: Number	26	21		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 30% pain responder

End point title	30% pain responder
End point description: Supportive outcome	
End point type	Other pre-specified
End point timeframe: 12 week	

End point values	Naltrexone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	50		
Units: Number	20	13		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: 50% pain responder

End point title	50% pain responder

End point description:

Supportive outcome

End point type	Other pre-specified

End point timeframe:

12 week

End point values	Naltrexone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	50		
Units: Number	12	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: January 6 2021 - December 27 2022	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups	
Reporting group title	Naltrexone
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Naltrexone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal ache	Additional description: Hospitalisation for 5 hours due to worsening of known abdominal pain		
subjects affected / exposed	0 / 49 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.01 %

Non-serious adverse events	Naltrexone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 49 (83.67%)	43 / 50 (86.00%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 49 (4.08%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			

subjects affected / exposed	18 / 49 (36.73%)	19 / 50 (38.00%)	
occurrences (all)	18	19	
Vivid dreams			
subjects affected / exposed	19 / 49 (38.78%)	9 / 50 (18.00%)	
occurrences (all)	19	9	
Dizziness			
subjects affected / exposed	14 / 49 (28.57%)	7 / 50 (14.00%)	
occurrences (all)	14	7	
General disorders and administration site conditions			
Hot flashes			
subjects affected / exposed	16 / 49 (32.65%)	7 / 50 (14.00%)	
occurrences (all)	16	7	
Dry mouth			
subjects affected / exposed	10 / 49 (20.41%)	10 / 50 (20.00%)	
occurrences (all)	10	10	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 49 (28.57%)	7 / 50 (14.00%)	
occurrences (all)	14	7	
Constipation			
subjects affected / exposed	8 / 49 (16.33%)	2 / 50 (4.00%)	
occurrences (all)	8	2	
Nausea			
subjects affected / exposed	13 / 49 (26.53%)	14 / 50 (28.00%)	
occurrences (all)	13	14	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	2 / 49 (4.08%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	5 / 49 (10.20%)	2 / 50 (4.00%)	
occurrences (all)	5	2	

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

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

The study was only powered to detect a difference between groups of 1.0 points. The results may not be generizable to men, older adults, adolescents, or different ethnic groups. No knowlegde about long term effects are provided from the trial.

Notes: