



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 efficacy | |

| 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 efficacy | |

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 occurrences (all) | 18 / 49 (36.73%) 18 | 19 / 50 (38.00%) 19 | |
| Vivid dreams subjects affected / exposed occurrences (all) | 19 / 49 (38.78%) 19 | 9 / 50 (18.00%) 9 | |
| Dizziness subjects affected / exposed occurrences (all) | 14 / 49 (28.57%) 14 | 7 / 50 (14.00%) 7 | |
| General disorders and administration site conditions | | | |
| Hot flashes subjects affected / exposed occurrences (all) | 16 / 49 (32.65%) 16 | 7 / 50 (14.00%) 7 | |
| Dry mouth subjects affected / exposed occurrences (all) | 10 / 49 (20.41%) 10 | 10 / 50 (20.00%) 10 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 14 / 49 (28.57%) 14 | 7 / 50 (14.00%) 7 | |
| Constipation subjects affected / exposed occurrences (all) | 8 / 49 (16.33%) 8 | 2 / 50 (4.00%) 2 | |
| Nausea subjects affected / exposed occurrences (all) | 13 / 49 (26.53%) 13 | 14 / 50 (28.00%) 14 | |
| Psychiatric disorders | | | |
| Depressed mood subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 1 / 50 (2.00%) 1 | |
| Metabolism and nutrition disorders | | | |
| Increased appetite subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 5 | 2 / 50 (4.00%) 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 generalizable to men, older adults, adolescents, or different ethnic groups. No knowledge about long term effects are provided from the trial. |
|---|

Notes: