



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 is a study with 1 arm only.

Currently the system cannot accommodate this specific scenario. Hence we had to work around 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 subjects affected / exposed occurrences (all) | Additional description: Vivid dreams or restlessness during sleep | | |
| | 2 / 27 (7.41%) 2 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 7 / 27 (25.93%) 7 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 27 (11.11%) 3 | | |
| Constipation subjects affected / exposed occurrences (all) | 2 / 27 (7.41%) 2 | | |
| Nausea subjects affected / exposed occurrences (all) | 3 / 27 (11.11%) 3 | | |
| Increased appetite subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | | |
| Psychiatric disorders | | | |
| Mood altered subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 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 anchors: 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: