Clinical Trial Protocol

FIbromyalgia and NALtrexone
The FINAL study

A randomized, double-blind, placebo-controlled trial

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1. General information:

The trial will be carried out according to this protocol, ICH-GCP guidelines, national regulatory requirements and legislation. The protocol is written following the recommendations given in the SPIRIT statement.

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Timeframe

Approval from authorities:	30.10.2019
Expected start of inclusion:	01.11.2020
Expected end of inclusion:	01.01.2023
Expected end of follow-up :	01.06.2023
Expected submission of papers:	01.01.2024

Abbreviations:

FM	=	Fibromyalgia
CSF	=	Cerebrospinal Fluid
ADL	=	Activities of Daily Living
NLX	=	Naltrexone
LDN	=	Low Dose Naltrexone
MS	=	Multiple sclerosis
TLR4	=	Toll-Like Receptor 4
Mg	=	Milligram
VAS	=	Visual analog scale
NRS	=	Numeric Rating Scale
RCT	=	Randomized Clinical Trial
SmPC	=	Summary of product characteristics
ED50	=	Effective dose in 50%
ED95	=	Effective dose in 95%
ACR1990	=	American College of Rheumatology 1990 classification criteria
FIQR	=	Revised Fibromyalgia Impact Questionnaire
PGI-I	=	Patient Global Impression of Improvement
VRS	=	Verbal Rating Scale
EQ-5D	=	EuroQol – 5 dimentions
EQ-VAS	=	EuroQol – visual analog scale
ACR-2016	=	The American College of Rheumatology 2016 revised criteria for FM
EMG	=	Electromyography
CPM	=	Conditioned pain modulation
TSP	=	Temporal summation of pain
CRP	=	C-reactive protein
ALAT	=	Alanine-aminotransferase
GFR	=	Glomerular-filtration-rate
hCG	=	Human chorionic gonadotropin
ECG	=	Electrocardiogram
PHQ-9	=	Patient Health Questionnaire – 9 item
GAD-7	=	Generalized Anxiety Disorder – 7 item
MCID	=	Minimal clinical important difference
PI	=	Primary Investigator
ID	=	Identity number
E-CRF	=	Electronic case report form
AE	=	Adverse Events
AR	=	Adverse Reactions
NSAID	=	Non Steroidal Anti-inflammatory Drug
SAE	=	Serious Adverse Events
SAR	=	Serious Adverse Reactions
SUSAR	=	Serious Unexpected Suspected Adverse Reactions
VAS	=	Visual analogue scale
Hz	=	Hertz
RMS	=	Root mean square
MPF	=	Amplitude and median power frequency
SMS	=	Short Message Service

2. Background

2.1 Background for the trial

Fibromyalgia (FM) is a condition characterized by chronic widespread pain and tenderness accompanied by symptoms like fatigue, sleep disturbances, cognitive disturbances, dysregulation of the autonomic nervous system, increased sensitivity to other sensory inputs, anxiety, depression etc. [1]. FM is a common disorder affecting approximately 2% of the general population [2]. Most often no pathology can be found in the tissue that can explain the pain, and evidence points to the fact that FM is caused by disturbances in central pain regulatory mechanisms [3, 4]. FM patients have been shown to have increased levels of enkephalins in the cerebrospinal fluid (CSF) [5] and decreased mu receptor availability has been demonstrated [6], suggesting that these patients also have a dysfunction in endogenous analgesia.

A key finding in patients with FM is widespread hyperalgesia to mechanical stimulation [7] and low pain thresholds for both mechanical and thermal stimulation [8, 9]. This can explain why FM patients have characteristic complaints of not only generalized pain but also generalized tenderness. Another predominant feature in FM is early muscular fatigue and intolerance to physical activity [10, 11], which can contribute to a debilitating decreased ability to perform activities of daily living (ADL). A previous study investigating muscular exhaustion in FM patients, have revealed a low correlation between perceived exhaustion and objective signs of muscle fatigue measured by electromyography, suggesting that also this symptom can be related to dysfunction in central regulatory mechanisms [12].

Naltrexone (NLX) has opioid receptor antagonistic effect [13], and it has been known for decades that NLX can have "paradoxical analgesic effect" when used in low doses [14]. In recent years low dose naltrexone (LDN) has been used widely as off-label treatment for pain and inflammation in multiple sclerosis (MS), Crohn's disease and fibromyalgia (FM) [15]. In Norway 0.3% of the general population has been shown to use LDN [16], the evidence is however sparse. The mechanisms of action of LDN are not fully understood, but could be regulation of homeostasis in the endorphin system, leading to enhanced endogenous analgesia and/or an anti-inflammatory effect mediated via blockade of toll-like receptor 4 (TLR4) leading to attenuation of central sensitization.

The proposed mechanisms of action of LDN are:

1) **Opioid Antagonism**
   In animal models chronic administration of naltrexone has been shown to increase expression of preproenkephalin mRNA 12-fold, leading to increased levels of enkephalins and increased density of opioid receptors in the brain [17]. This is thought to enhance endogenous analgesia [18].
2) **Toll-like Receptor 4 (TLR4) blockade in astrocytes and glia cells**
   In response to pain, astrocytes and microglia cells can initiate a proinflammatory cytokine cascade, thought to be involved in the development and maintenance of chronic pain [19]. LDN blocks TLR4 and human studies have demonstrated that LDN reduces the level of proinflammatory cytokines in FM patients [20]. Targeting TLR4 is a new emerging therapeutic field that holds promise as disease-modifying and opioid-sparing alternatives for persistent pain states [21]

Since no specific pharmacological treatments of FM is available, the existing pharmacological agents aims at either reducing facilitatory neurotransmitters (e.g. gabapentinoids), or increasing inhibitory neurotransmitters (e.g. Serotonin Norepinephrine Reuptake Inhibitors) [22]. LDN might

be a new disease modifying therapy that could potentially reduce neuroinflammation and induce homeostasis in the endorphin system in FM patients.

2.2 Summary of results from previous LDN-related clinical trials

Only 2 small placebo-controlled studies have investigated the effect of LDN on FM.
The first study was a single blind, observational prospective cohort study with participation of only 10 women with FM [23]. The participants received placebo for 2 weeks, followed by 8 weeks treatment with LDN 4.5 mg. The primary endpoint was self-reported overall fibromyalgia symptoms during the last 24 hours, on a 0-100 visual analog scale (VAS). FM symptoms were averagely reduced by 32.5% during treatment with LDN, and 2.3% during placebo treatment. Sixty percent (6/10) were classified as responders, having more than a 30% reduction of their FM symptoms.

The same research team later carried out a small placebo controlled randomized clinical trial (RCT) with participation of 31 women with FM [24]. It was designed as a crossover study, and participants were randomized to either 4 weeks of placebo followed by 12 weeks of treatment with LDN 4.5 mg, or 12 weeks of treatment with LDN 4.5 mg followed by 4 weeks of placebo. Primary endpoint was average pain during the last 3 days rated on a 0-100 VAS. The average reduction of pain was 28.8% when treated with LDN and 18% when treated with placebo. The between-group difference was significant (P = 0,016).Thirty-two percent of the subjects receiving LDN were classified as responders, defined as having a minimum 30% reduction of pain plus a minimum of 30% improvement of fatigue or sleep. In the placebo group the response rate was 11%. The differences in response rates were significant.

2.3 Background information about Naltrexone

NLX is marketed as an additional therapy for supporting abstinence in patients with previous abuse of opioids or alcohol, and doses of 50 mg/day is traditionally used [25]. NLX is primarily known for its antagonistic effect on the opioid receptor [13], but is also thought to blunt dopaminergic transmission in mesolimbic pathways, thereby attenuating craving and reinforcing effects of alcohol [26]. NLX has the same biochemical structure as Naloxone, but has a higher oral bioavailability and a longer half-life [27].

2.4 Known and potential side effects, risks and possible benefits for the subjects

Risks:

In several clinical studies LDN has been shown to be well tolerated when used for treatment of FM, MS or Crohns disease [15]. No serious adverse events have been reported in any of the clinical studies of LDN. Possible side effects of Naltrexone 50 mg is listed in the Summary of Product Characteristics (SmPC) below. In this study a dose of 6 mg is used, and the risk of serious adverse events when using this low dose is considered to be minimal.

Benefits:

Potential benefits for the participants are that they might experience reduced tenderness, reduced pain, improved sleep, improved energy and improvement in daily functioning. All participants will be offered treatment with LDN in an individual dosing after termination of the trial. The results from the study will be of benefit for other patients with FM.

SmPC for Naltrexone 50 mg:

The following undesirable effects are ranked according to system organ class and to their frequency:

Very common (≥ 1/10)

Common (≥1/100 to < 1/10)

Uncommon (≥1/1,000 to < 1/100)

Rare (≥ 1/10,000 to < 1/1,000)

Very rare (< 1/10,000)

not known (cannot be estimated from the available data)

MedDRA system organ class	
Infections and infestation	
Uncommon	Oral herpes
	Tinea pedis
Blood and lymphatic system disorders	
Uncommon	Lymphadenopathy
Rare	Idiopathic thrombocytopenic purpura
Metabolism and nutrition disorders	
Common	Decreased appetite
Psychiatric disorders:	
Very common	Nervousness
	Anxiety
	Insomnia
Common	Affective disorders
	Despondency
	Irritability
	Mood swings
Uncommon	Hallucination
	Confusional state
	Depression
	Paranoia
	Disorientation
	Nightmare
	Agitation
	Libido disorder
	Abnormal dreams
Rare	Suicidal ideation

	Attempted suicide
Very rare	Euphoria
Nervous system disorder	
Very common	Headache
	Sleep disorders
	Restlessness
Common	Dizziness
	Shivering
	Vertigo
Uncommon	Tremor
	Somnolence
Rare	Speech disorder
Eye disorders	
Common	Lacrimation increased
Uncommon	Vision-blurred Eye irritation
	Photophobia
	Eye swelling
	Eye pain
	Asthenopia
Ear and labyrinth disorders	
Uncommon	Ear discomfort
	Ear pain
	Tinnitus
	Vertigo
Cardiac disorders	
Common	Tachycardia
	Palpitations
	Electrocardiogram change
Vascular disorders	
Uncommon	Blood pressure fluctuation
	Flushing
Respiratory, thoracic and mediastinal disorder	
Common	Chest pain
Uncommon	Nasal congestion
	Nasal discomfort
	Rhinorrhea

	Sneezing
	Oropharyngeal pain
	Sputum increased
	Sinus disorder
	Dyspnoea
	Dysphonia
	Cough
	Yawning
Gastrointestinal disorder	
Very common	Abdominal pain
	Abdominal cramps
	Nausea or Inclination to vomit
	Vomiting
Common	Diarrhoea
	Constipation
Uncommon	Flatulence
	Haemorrhoids
	Ulcer
	Dry mouth
Hepatobiliary disorders	
Uncommon	Liver disorder
	Blood bilirubin increased
	Hepatitis
	During treatment an increase of liver transaminases may occur. After discontinuation of Naltrexone the transaminases decreased to baseline within several weeks.
Skin and subcutaneous tissue disorder	
Common	Rash
Uncommon	Seborrhoea
	Pruritus
	Acne
	Alopecia
Very rare	Exanthema
Musculoskeletal and connective tissue disorders :	
Very common	Arthralgia

	Myalgia
Uncommon	Groin pain
Very Rare	Rhabdomyolysis
Renal and urinary disorders	
Common	Urine retention
Uncommon	Pollakiuria
	Dysuria
Reproductive system and breast disorders	
Common	Delayed ejaculation
	Erectile dysfunction
General disorder and administration site conditions	
Very common	Feebleness
	Asthenia
Common	Lack of appetite
	Thirst
	Energy increased
	Chills
	Hyperhidrosis
Uncommon	Increased appetite
	Weight loss
	Weight gain
	Pyrexia
	Pain
	Peripheral coldness
	Feeling hot

2.5 Description and justification of dose, dosing regimen and treatment period.

In previous clinical trials one daily dose of 4.5 mg LDN has been tested. One daily dosing will lead to an intermittent blockade of mu receptors, and it has been suggested that this intermittent blockade is important for LDN to exert its regulation of the homeostasis in the endorphin system in the brain.

To be able to choose a dose that is both sufficiently effective and tolerable in as many patients as possible, our research group has conducted a dose-response study prior to this study (paper in press). Subjects included in the study were women aged 18-60 with a diagnose of FM. In the dose-response study we found that 3.88 mg was the dose effective in 50% (ED50) and 5.4 mg was the dose effective in 95% (ED95). In the dose-response study, doses higher than 6 mg was not tested and we did not find problems with safety or tolerability using doses up to 6 mg. Based on these findings we conclude that 6 mg is an appropriate test dose.

From previous clinical trials it has been shown that pain is reduced with more than 30% in 57-60% of FM patients after 8-12 weeks of treatment with LDN [24]. In a clinical trial investigating immune effects of LDN, proinflammatory cytokines was significantly reduced after 8 weeks of treatment with LDN [20].

Thus, based on results from previous clinical trials, we have chosen the treatment period in this study to be 12 weeks including a titration phase of 4 weeks (i.e. 4 first weeks of the 12 week period).

2.6 Description of the study population

The study population will consist of female participants (age 18-64 years), who fulfills the classification criteria for FM according to the American College of Rheumatology 1990 (ACR1990) [7].

3. Aim of the study

3.1 Hypothesis:

LDN treatment will be superior in reducing pain in FM patients compared with placebo.

3.2 Aims and objectives:

The aim of the trial is to investigate whether treatment with LDN has a superior effect compared to placebo on pain among female patients with fibromyalgia, evaluated after 12 weeks of treatment. In the study we will also explore secondary aims regarding a possible improvement of other FM core symptoms.

Our primary efficacy objective will be to compare the effect of drug LDN, relative to placebo, on changes in average pain during the last 7 days, from baseline to week 12, in female patients with fibromyalgia.

Our key secondary efficacy objectives will be to compare the effect of drug LDN, relative to placebo, on *(i)* global assessment and on *(ii)* changes in pain, *(iii)* tenderness, *(iv)* fatigue, *(v)* sleep disturbance, *(vi)* depression, *(vii)* anxiety, *(viii)* cognition, *(ix)* stiffness, *(x)* physical function, *(xi)* quality of life and *(xii)* pain distribution from baseline to week 4, 8 and 12, in female patients with fibromyalgia. Furthermore, responder indices will be compared between the treatment groups.

Among the exploratory secondary objectives are changes in muscle exhaustion, physical fitness, pain sensitivity, inhibition of pain, augmentation of pain, and pro-inflammatory cytokines.

4. Plan for the study

4.1 Primary and secondary end-points

Primary end-point:

- Average pain during the last 7 days. Change from baseline when assessed after 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Assessed by asking the participants about the level of average pain during the last 7 days on a 11 point rating scale (ranging from “no pain” to “unbearable pain”) using the first item from the symptom part of the Fibromyalgia Impact Questionnaire Revised (FIQR) [28]

Key Secondary end-points:

- Global assessment. Change in overall fibromyalgia symptoms from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Measured by Patient Global Impression of Change (PGI-C) on a 1-7 Verbal Rating Scale (VRS). The participants are asked how they rate their overall fibromyalgia symptoms after 4, 8 and 12 weeks of treatment compared with before treatment. A score of 4 indicates “no change”, a score of 1 is characterized by “a lot worse” and a score of 7 is characterized by “a lot better”.
- Impact of fibromyalgia. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Measured by the FIQR total score. The FIQR asks patients to rate how difficult it is to perform a list of 9 common activities over the previous 7 days on an 11 point scale (ranging from "no difficulty" to "very difficult"). The FIQR then asks patients to indicate how often their fibromyalgia impacts their quality of life over the last 7 days on an 11 point scale (ranging from "never" to "always"). Finally, the FIQR asks patients to assess the severity of 10 different symptoms on an 11 point scale (ranging from no symptoms to extreme symptoms). These three sub-scales are summed to represent an overall FIQR score. A lower score indicates lower severity.
- Health-related quality of life. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Measured by EuroQol-5D (EQ-5D) and EuroQol-VAS (EQ-VAS) [29]. The EQ-5D measures 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Every domain is rated on a 1-5 VRS, a score of 1 indicating no problems, and a score of 5 indicating extreme problems. The EQ-VAS asks the participant to rate their overall health ‘today’ on a 0-100 VAS.
- Pain distribution. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Assessed by the Widespread Pain Index (WPI) from The American College of Rheumatology 2016 revised criteria for FM (ACR-2016) [30]. The body is divided into 19 body parts and number of pain full body parts during the last 7 days is counted, giving rise to the WPI.
- Level of pain. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference. Assessed by the FIQR “level of pain” question, asking the participants to rate the average level of pain during the last 7 days on a 11 point rating scale (ranging from “no pain” to “unbearable pain”)
- Level of tenderness. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Assessed by the FIQR “level of tenderness to touch” question, asking the participants to rate the average level of tenderness to touch during the last 7 days on an 11 point rating scale (ranging from “no tenderness” to “very tender”).
- Pain threshold. Change from baseline when assessed after 12 weeks of treatment with LDN or LDN-placebo. Assessed using a handheld algometer. Points measured: Right Quadriceps 15 cm proximal of apex patella and left Trapezius 10 cm from acromion. Each point is measured 3 times.
- Level of fatigue. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Assessed by the FIQR “level of energy” question, asking the participants to rate the average level of energy

during the last 7 days on an 11 point rating scale (ranging from “lots of energy” to “no energy”).

- Level of Sleep disturbance. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Assessed by the FIQR “quality of sleep” question asking the participants to rate the average quality of sleep during the last 7 days on an 11 point rating scale (ranging from “awoke well rested” to “awoke very tired”).
- Level of depression. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Assessed by the FIQR ”level of depression” question, asking the participants to rate the average level of depression during the last 7 days on an 11 point rating scale (ranging from “no depression” to “very depressed”).
- Level of anxiety. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Assessed by the FIQR “level of anxiety” question, asking the participants to rate the average level of anxiety during the last 7 days on an 11 point rating scale (ranging from “not anxious” to “very anxious”).
- Level of Cognition. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Assessed by the FIQR “level of memory problems” question, asking the participants to rate the average level of memory problems during the last 7 days on an 11 point rating scale (ranging from “good memory” to “very poor memory”).
- Level of Stiffness. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Assessed by the FIQR “level of stiffness” question, asking the participants to rate the average level of stiffness during the last 7 days on an 11 point rating scale (ranging from “no stiffness” to “severe stiffness”)
- Level of Physical function. Change from baseline when assessed after 4, 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Assessed by the physical function domain of FIQR; asking patients to rate how difficult it is to perform a list of 9 common activities over the previous 7 days on an 11 point scale (ranging from "no difficulty" to "very difficult"). The score is characterized by the sum of the 9 scores (0-90), a lower score indicates better function.
- Number of responders with a more than 15% improvement of the primary outcome. (Number of responders are calculated for both the LDN and the LDN-placebo group)
- Number of responders with a more than 30% improvement of the primary outcome. (Number of responders are calculated for both the LDN and the LDN-placebo group)
- Number of responders with a more than 50% improvement of the primary outcome. (Number of responders are calculated for both the LDN and the LDN-placebo group)

Exploratory secondary end-points:

- Variation in pain. Change from baseline when assessed after 8, and 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Measured using a diary of daily average pain rated on an 11 point rating scale during 7 days before visits at baseline, and after 8 and 12 weeks of treatment. The variation in pain is characterized by the highest score minus the lowest score during the 7 days.

- Muscle exhaustion. Change from baseline when assessed after 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Measured by an isometric muscle exhaustion test of the deltoid muscle as described under section 6.3. in this protocol.
- Physical fitness. Change from baseline when assessed after 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Measured by the 30-second chair stand test as described under section 6.3 in this protocol.
- Pain sensitivity. Change from baseline when assessed after 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Measured by cuff-algometry as described under the section 6.3 in this protocol.
- Inhibition of pain. Change from baseline when assessed after 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Measured by Conditioned pain modulation (CPM) as described under section 6.3 in this protocol.
- Augmentation of pain. Change from baseline when assessed after 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Measured by Temporal Summation of Pain (TSP) as described under section 6.3 in this protocol
- Inflammation. Change in level of cytokines from baseline when assessed after 12 weeks of treatment with LDN or LDN-placebo (between-group difference). Measurement of levels of pro-inflammatory cytokines in plasma or serum is carried out.

Data collected at baseline:

- Demographic data
- Concomitant medicine
- Serum levels of C-reactive protein (CRP), bilirubin, Alanine-aminotransefase (ALAT), creatinine, Glomerular-filtration-rate (GFR), thrombocyte count
- Electrocardiogram (ECG)
- Vital signs (Blood pressure, weight, height)
- Urine – Human chorionic gonadotropin (hCG)
- Patient Health Questionnaire – 9 item (PHQ-9) [31]
- Generalized Anxiety Disorder – 7 item (GAD-7) [32]

4.2 Description of study design

The study is designed as a parallel randomized (1:1) double blind, placebo-controlled superiority trial.

4.3 Sample size and power calculation

We used values from our previous dose-response study, and determined that the self-reported pain on a 0-10 NRS at baseline had a mean of 6.7 with a standard deviation of 1.5 NSR units. According to IMMPACT guidelines a minimal clinical important difference (MCID) is defined as a 15% decrease in pain. An improvement of the patients' condition corresponding to a 15% decrease on average in pain is equivalent in the present patient group to a reduction of 1.0 on a 0-10 NRS [33]. With a power of 0.80 and a significance level of 0.05 we will need 74 patients, 37 patients in each group, to demonstrate a between-group difference equivalent to at least 15% improvement on the between-group change score (i.e. a difference between groups of 1.0 NRS units). Expecting some attrition and drop-out for the 12 weeks trial period it was decided to include 100 patients, in the total intention-to-treat (ITT) population (50:50), corresponding to a statistical power of more than

90% anticipating that they all remain in the ITT population. Thus 100 patients will be randomized to treatment with LDN or placebo for 12 weeks, with 50 participants in each arm.

4.4 Measures for reduction of bias

The RCT study is triple blinded, meaning that participating patients, investigators, outcome assessors and statistical analysts are all blinded regarding the allocation. After baseline all questionnaire data will be filled in by the patient via an electronic survey prior to the visits. An independent assessor will perform all protocol specific procedures after baseline. Unblinding will first take place after primary analysis of the data has taken place.

A data manager, otherwise not involved in the study, will create a randomization list, using a computerized algorithm. The randomization list will be sent to the Hospital Pharmacy Funen, who will label the medicine with blinding codes according to this list. The active medicine and placebo tablets will look similar and will be blinded in similar cans. The medicine will be shipped to the place of the trial together with individual code-envelopes for every blinding code. A copy of the randomization list will be stored behind double lock at the office of the sponsor.

In case of a SUSAR the participating patients will be unblinded by sponsor before reporting to the Danish Medicines Agency. Primary investigator (PI) remains blinded.
Primary investigator is only unblinded in case of a medical emergency, and only if PI finds it necessary to ensure the safety of the subject. PI can unblind a single subject by breaking the code-envelope related to the subjects blinding code. The code-envelopes will be stored together with the trial medication at the site of the trial and can be accessed 24/7. In case of unblinding of Primary investigator this is documented in the patients file. If a code-envelope is opened, it is stored in the trial master file.

4.5 Description of the treatment in the study

After inclusion the participants are randomized according to the abovementioned procedure to receive either placebo or LDN for 12 weeks. 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.

The active LDN-medicine and LDN-placebo is manufactured at Glostrup Pharmacy and shipped to Hospital Pharmacy Funen, where it is canned and labeled. The trial medicine will be labeled with blinding codes according to the randomization list by Hospital Pharmacy Funen. Before handing out the trial medication, the ID-number of the subject will be written on the medicine cans. The trial medicine is taken once daily in the evening, between 7 pm and 11 pm.

4.6 Description of expected timeframe for the individual participant

The timeframe for the study is 16 weeks. This includes a 12 week intervention period (week 0 to 12) and a 4 week follow-up period (week 12 to 16).

4.7 Rules for termination the study

The participants will be withdrawn from the study in case of:

- Serious adverse reactions
- If the subject wants to withdraw
- If changes in the participants other pain medication occur during the trial

However, we will attempt to contact all patients corresponding to closure of the trial, since no statistical approaches for imputation of missing data can compete with the real patient data.

If the intended sample size is not reached at 30 months after recruitment has started, the inclusion of patients will stop at 74 patients, which will ensure a power of 80%.

4.8 Procedures for accounting for the trial medicine, including placebo products

The study medicine and the placebo tablets are prepared at Glostrup Pharmacy. The study medication is shipped from Glostrup Pharmacy to the Hospital Pharmacy Funen, where it is canned and labeled. Hospital Pharmacy Funen will provide the medicine cans with a blinding code according to the randomization list. The study medicine will be delivered together with code-envelopes from the Hospital Pharmacy Funen to the place of the trial (Pain Centre South), where the medicine is stored in a locked medicine deposit room. The medicine is stored in a separate shelf, clearly separated from other medicine. When the study medication is received, a receipt is made as recommended by the GCP unit. A copy of the randomization list is stored by Sponsor behind double lock. The individual code-envelopes are stored together with the trial medication.

Participants included in the study will receive an ID-number and the subjects will be randomized to placebo or active treatment. Both ID-number and blinding code is documented in the patient medical file. The ID-number is written on the medicine cans at the site of the trial.

The participants are treated with active medicine or placebo for 12 weeks. Trial medication is handed out at baseline (week 0). The first 4 weeks of treatment the dose is titrated up, starting with 1.5 mg and increasing the dose with 1.5 mg every seventh day up to 6 mg. At the visits during the intervention phase, empty medicine-cans for the previous period will be returned and any non-ingested medicine will be counted. Participants will be asked at every visit if they lost any of the tablets. Both number of returned tablets and number of lost tablets will be documented.

4.9 Source data

Source data that appears from the electronic case report form (E-CRF) are demographic data, questionnaire data, adverse events (AE) and adverse reactions (AR) and data from protocol specific procedures: Pain threshold, pain sensitivity, CPM, TSP and 30-second chair stand test.
Source data from the isometric muscle exhaustion test will be stored in a secure Sharepoint.
Source data that appears from the subjects file are data about concomitant medicine and laboratory data (blood tests and ECG).

5. Selection and withdrawal of participants

5.1 Selection and screening of subjects

Patients are recruited from a pain clinic at Odense University Hospital and through advertising in relevant written and internet media. Participants recruited from the pain clinic will receive written information from their physician or nurse. Participants that respond through advertisement will receive written information material by e-mail about the trial. All participants will afterwards receive a telephone call where oral information will be given. Participants that are interested in participating will be seen at a screening interview to establish whether they fulfill the in- and exclusion criteria. Written informed consent is given at the beginning of the screening interview.

5.2 Inclusion criteria

The following inclusion criteria are applied:

- Women aged 18-64 years
- Understands and writes Danish
- Fulfills the ACR1990 criteria for FM
- A minimum score of 4 in self-reported average pain during the last 7 days on a 0-10 NRS at baseline
- All fertile women have to use safe anti conception (Spiral, birth control pills, contraceptive patch, contraceptive vaginal ring or gestagen injections) for 3 weeks before and 1 week after the trial. If the participants' normal lifestyle includes sexual abstinence, they do not have to use anti conception. Instead they can give an oral informed consent, that they will be sexually abstinent during the trial. A woman is considered non-fertile if she is sterilized, hysterectomized, bilateral oophorectomized or is postmenopausal. A woman is considered postmenopausal when vaginal bleeding has been absent for 1 year and is confirmed by measurement of follicle-stimulating hormone.

5.3 Exclusion criteria

The following exclusion criteria are applied:

- Known allergy against naltrexonehydroclorid
- Pregnancy or breastfeeding. A negative pregnancy test has to be available for all fertile subjects at baseline
- Use of opioids or NSAIDs up to 4 weeks before inclusion in the trial
- Known abuse of alcohol or other substances
- Known inflammatory rheumatic diseases
- Known demyelinating diseases
- Known active cancer
- Liver dysfunction (ALAT must not be elevated more than 2-fold over highest reference level)
- Kidney dysfunction (GFR < 59 mL/min)
- Psychotic diseases
- History of suicide attempts
- Suicide ideation – evaluated using PHQ-9 (Item 9 has to be answered "never")

5.4 Procedures for withdrawal

A participant will be withdrawn from the study:

1) In case of SAR. Participants will be instructed to cease the treatment immediately if a SAR is suspected. Follow-up is made regularly until the symptoms are resolved or stable.
2) In case of non-compliance. The participants will receive the trial medicine for 12 weeks. Trial medicine is handed out for 4 weeks at a time. Visits are performed at screening, at baseline (week 0), after 2, 4, 8, 12 weeks of treatment and 4 weeks after end of trial. The visit at week 2 is a telephone visit. Empty medicine-cans are returned at follow-up visits. Medicine that has not been ingested is counted and any loss of medicine is reported. The participant is considered non-compliant if adherence to the medication is less than 80%.
3) If major changes to the participants concomitant pain medication is needed during the 12 weeks of treatment. At every visit the patients shared medication record is updated. If any change in dosing of current pain medication or any new pain medication is registered, the participant is withdrawn from the study.
4) If the participant wants to withdraw. If the participant at any time during the trials wants to cease the treatment, the participant is withdrawn from the study.

All participants that are withdrawn from the study will be encouraged to complete all visits as scheduled. Participants that are withdrawn will not be replaced. According to our sample size calculation, we will include participants enough to tolerate a drop-out rate of up to 25%. Data will be collected from participants that are withdrawn and relevant data will be analyzed. Both intention to treat and per protocol analysis will be performed and compared to assess the robustness of the primary analyses.

6. Treatment of participants

6.1 Description of the treatment

The participants will receive trial medication in a total of 12 weeks. The medicine is ingested once daily in the evening between 7 PM and 11 PM. The participants are randomized to receive either active treatment with 6 mg LDN or placebo. After termination of the study, the participants are offered treatment with LDN in an individualized dosing.

Screening visit (week -4 to 0):

- Informed consent
- ECG
- Blood testing
- Urine-hCG
- Physical examination
- Medical history
- Medication history
- Demographic data
- PHQ-9 and GAD-7
- Adverse events
- Subjects are assessed if they meet the in- and exclusion criteria

Randomization (week 0):

- Medication history
- PROMs
- Vital signs
- Urine-hCG
- Adverse events
- Algometry
- Cuff-algometry
- CPM/TSP
- 30-second chair stand test
- Muscle exhaustion test
- Randomization to LDN or placebo
- Hand out of medicine for the titration phase weeks 1-4, treatment phase weeks 5-8 and treatment phase weeks 9-12 in three separate cans.

Telephone visit – titration phase (week 2 +/- 2 days)

- Adverse events
- Compliance assessment

End of titration - telephone (week 4 +/- 2 days)

- Medication history
- PROMs
- Urine-hCG (measured at home)
- Adverse events

Follow up visit – telephone (week 8 +/- 7 days): Medication history

- Medication history
- PROMs
- Urine-hCG (measured at home)
- Adverse events

End of trial (week 12 +/- 7 days):

- Return of empty medicine cans
- Assessment of compliance
- Medication history
- PROMs
- Vital signs
- Urine-hCG
- Adverse events
- Algometry
- Cuff-algometry
- CPM/TSP
- 30-second chair stand test
- Muscle exhaustion test
- ECG
- Blood testing

End of follow-up visit - telephone (week 16 +/- 7 days):

- Medication history
- PROMs
- Adverse events

6.2 Visit schedule

Study phase	Screening	Intervention					End of follow-up
		Randomization	Up-titration		Follow-up	End of trial	
Week	-4 to 0	0	2* +/- 2 days	4* +/- 2 days	8* +/- 7 days	12 +/- 7 days	16* +/- 7 days
Eligibility screening	x						
Informed consent	x						
Physical examination	x						
Medical history	x						
PHQ-9 and GAD-7	x						

Medication history	x	x	x	x	x	x	x
Blood testing	x					x	
ECG	x					x	
Vital signs		x				x	
Urine-hCG	x	x		x**	x**	x	
PROMs		x		x	x	x	x
Computerized cuff algometry		x				x	
Handheld pressure algometry		x				x	
CPM/TSP		x				x	
Muscle exhaustion test		x				x	
30s stand chair test		x				x	
Medicine allocation		x					
Medicine hand-out		x					
Compliance assessment						x	
Adverse events		x	x	x	x	x	x

*Telephone visit
**Urine-hCG is measured at home

6.3 Protocol specific procedures

Key secondary outcomes:

Level of Tenderness: Measured using a handheld pressure algometer. Points measured is right quadriceps 15 cm from apex patella, and left trapezius 10 cm acromion (between acromion and C6/7). Each point is measured 3 times; point 2 and 3 is measured 1 cm above and 1 cm below the first point.

Exploratory secondary outcomes:

Pain Sensitivity: Standardized assessment of experimental pressure pain sensitivity is performed at baseline and after 12 weeks of treatment. Assessments are conducted as recommended by the 'International Association for the Study of Pain'. Computer-controlled cuff algometry is performed on lower legs in all patients to assess pressure pain threshold and pressure pain tolerance.

Inhibition (CPM) and augmentation (TSP) of pain: Standardized assessment of experimental efficiency of the pain modulatory systems is performed at baseline and after 12 weeks of treatment. Assessments are conducted as recommended by the 'International Association for the Study of Pain'. Computer-controlled cuff algometry is performed on lower legs in all patients to assess temporal summation of pain (TSP: increase in pain scores to ten repeated stimulations), and conditioned pain modulation (CPM: increase in pressure pain threshold during cuff pain conditioning on the contralateral leg).

Standardized assessment of experimental pressure pain sensitivity has shown good reliability, and provides insights into the pathophysiological mechanisms involved in the pain condition.

Muscular exhaustion: Measured by asking the participant to complete an isometric muscle exhaustion task by maintaining 90° shoulder abduction (dominant arm) for as long as possible with the elbow extended and the hand pronated (hand facing downwards). The participants will be seated on a chair without armrests and both feet placed on the floor. An observer will assess the quality of the test by looking for compensations (e.g. shoulder shrugging or lateral flexion of trunk) and correct the participant. Task failure (test position can no longer be maintained) defines the test duration. The participants are instructed to maintain the position until they feel maximal muscle exhaustion (corresponding to a score of 10 on a 0-10 scale with 0 being "no muscle fatigue" and 10 being 'maximal muscle fatigue/exhaustion'). Before and immediately after the test, the participants are asked to rate the current shoulder pain intensity on a 0-100 visual analogue scale (VAS), with anchors 0 = "no pain" and 100 = "worst pain". Surface electromyography (EMG) will be recorded from the anterior, middle and posterior deltoid muscle at 3000 Hz during the entire test. From the EMG recordings during the exhausting test the root mean square (RMS) amplitude and median power frequency (MPF) will be calculated in 1 second epochs, using a fast Fourier transform algorithm. The 1 second epochs will be normalised against their respective initial values (iMPF and iRMS), calculated as the mean of the first 5 seconds and set to 100%. Normalised MDF (nMPF) and RMS amplitudes (nRMS) at 50% of test duration (halfway +/- 2.5 seconds) will be calculated as a percentage of the initial values (iMPF and iRMS). nMPF and nRMS at the end of the test (exhaustion) will be calculated as the mean of the last 5 seconds.
Outcomes measured:

1) Duration of the test (from start to exhaustion)
2) Change in shoulder pain intensity (0-100 visual analogue scale) from before to immediately after the test
3) Change from first 5 seconds to last 5 seconds in surface EMG nRMS
4) Change from first 5 seconds to last 5 seconds in surface EMG nMPF
5) Change from first 5 seconds to middle 5 seconds in surface EMG nRMS
6) Change from first 5 seconds to middle 5 seconds in surface EMG nMPF

Physical fitness: Measured by the 30 second chair stand test. The test starts with the subject seated on a chair with her back touching the backrest. Subjects rise to a full stand with the back straight and then sit down again to regain this cycle as many times as they can within 30 seconds. Arms have to be crossed over the chest during the test. Before the test, subjects are asked to perform one repetition to familiarize with the procedure.

Biological material

Blood for a bio bank will be collected at baseline and after 12 weeks of treatment. There will be stored 2 x 0.5 ml serum and 2 x 0.5 ml plasma in the bio bank collected at both baseline and after 12 weeks of treatment, for later analysis of inflammatory cytokines.

6.4 Rules for concomitant medication/treatment during the trial

The participants are not allowed to use opioids, NSAIDs or medication with anti-inflammatory effects. The participants are allowed to continue with paracetamol, pregabalin, gabapentin, antidepressants, baclofen or tizanidin but the dosing must remain stable 4 weeks before and during the trial. The participants are not allowed to receive any new pain medication during the trial.

6.5 Measures to promote compliance

Participants will receive a daily SMS reminder about taking their trial medication. At all visits, empty medicine cans are returned and non-ingested tablets are counted. The participants are considered non-compliant if the trial medication is not taken at least 80% of the trial period.

6.6 Treatment of subjects after termination of the study

At the follow-up visit, future treatment can be discussed with the primary investigator, and treatment with LDN in an individual dosing is offered.

7. Outcome measures

7.1 Specification and justification of outcome measures

Previous studies have found that 57-60% of patients with FM treated with LDN for 8-12 weeks report a more than 30% decrease in pain. We have chosen change in pain intensity between baseline and 12 weeks of treatment, measured on a 0-10 NRS (FIQR item) to be the primary outcome.

As key secondary outcomes we have chosen other core FM symptoms/domains as recommended by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) guidelines [34]. These symptoms/domains constitutes: Impact of fibromyalgia, level of pain, level of tenderness, level of fatigue, level of sleep disturbance, level of depression, level of anxiety, level of stiffness, level of cognition and level of physical function. These symptoms/domains are evaluated based on single FIQR items, FIQR subscales and FIQR total score. Level of tenderness is also assessed using a handheld pressure algometer. FIQR is a validated questionnaire often used to evaluate symptom burden and fluctuations in the disease of FM [28]. The FIQR asks patients to rate how difficult it is to perform a list of 9 common activities over the previous 7 days on an 11 point scale (ranging from "no difficulty" to "very difficult"). The FIQR then asks patients to indicate how often their fibromyalgia impacts their quality of life over the last 7 days on an 11 point scale (ranging from "never" to "always"). Finally, the FIQR asks patients to assess the severity of 10 different symptoms on an 11 point scale (ranging from no symptoms to extreme symptoms). These three sub-scales are summed to represent an overall FIQR score. A lower score indicates lower severity. Other key secondary outcomes are global assessment, pain distribution, pain sensitivity and health-related quality of life. Global assessment will be made using the PGI-C scale. Pain distribution will be measured using the Widespread Pain Index (WPI). Assessments of pain sensitivity are conducted as recommended by the 'International Association for the Study of Pain.' EQ-5D is a validated instrument used to measure quality of life in both population based studies and in the study of various acute and chronic diseases [35].

Exploratory secondary outcomes are changes in muscular exhaustion, physical fitness, pain inhibition, pain augmentation and level of inflammatory cytokines. From the clinical experience with LDN, patients often report improvement of early muscular fatigue and better daily functioning. To be able to evaluate such possible effects we have chosen to include some explorative outcome parameters. Effect on daily functioning will be evaluated using the function domain of the FIQR. To evaluate a possible improvement of muscular exhaustion and physical fitness a muscular exhaustion test of the deltoid muscle [12] and a 30-second chair stand test will be carried out [36]. Assessments of pain inhibition and pain augmentation are conducted as recommended by the 'International Association for the Study of Pain.' Level of relevant pro-inflammatory cytokines will be measured.

7.2 Methods and times for measurement, registering and analysis of outcome measures
Demographic data are collected at screening.
Questionnaire data for phenotyping of patients are collected at screening (PHQ, GAD).
Questionnaire data that are used as outcome measures are collected at baseline (week 0) and after 4, 8 and 12 weeks of treatment and at follow up (FIQR, EQ-5D, PGI-C, ACR2016).
Protocol specific procedures: Pain sensitivity, CPM/TSP, 30-second chair stand test and muscle exhaustion test of the deltoid muscle are measured at baseline and after 12 weeks of treatment.
Blood tests and ECG are collected at screening and after 12 weeks of treatment.
Safety data are collected at all visits

When the trial is terminated, and primary statistical analysis has been performed the investigators are unblinded. Changes in outcome measures are compared between the active versus the placebo group.

8. Safety evaluation

8.1 Specification and justification of safety parameters
As mentioned in section 2.4 the study medication is considered safe to use and the risk of serious adverse drug reactions is considered to be very small. Liver function and kidney function is monitored during the trial, measuring ALAT, bilirubin, Creatinine and GFR at screening and after 12 weeks of treatment. Thrombocyte function is measured at screening and after 12 weeks of treatment. Heart function is monitored by measuring ECG at screening and after 12 weeks of treatment. Urine-hCG is measured with a sensitivity of minimum 25 mIU/ml at baseline (week 0) and after 4, 8 and 12 weeks of treatment in all fertile women. At 4 and 8 weeks, the participants will take the pregnancy test at home.

8.2 Procedures for registration and reporting of adverse events/adverse reactions
Definitions:

- Adverse event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment
- Adverse reaction (AR): All untoward and unintended responses to an investigational medicinal product related to any dose administered.
- Unexpected adverse reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).
- Serious adverse event (SAE) or serious adverse reaction (SAR): any untoward medical occurrence or effect that at any dose results in death is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
- Serious unexpected suspected adverse reactions (SUSAR): an adverse reaction that is both unexpected and serious

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 SmPC for Naltrexone 50 mg is used as reference document when assessing AE and AR.

8.3 Arrangements for avoiding and treating complications
Complications as a result of the treatment are not expected.

8.4 Statement of how and how long the trial participants should be monitored in case of adverse events/adverse reactions
The participants are offered follow up at the primary investigator until adverse events/adverse reactions have ceased or are stable.

8.5 Reporting of suspected unexpected serious adverse reactions

- Investigator must report all serious adverse events (SAE) to sponsor immediately but no later than 24 hours after the event. All SAE's are registered in a SAE formula which is sent without delay to sponsor by e-mail. In the SAE formula investigator will also report suspected causality.
- Causality of a SAE shall be determined according to CT-3 guidelines. All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the sponsor should be provided with the report.
- If a SAR is assessed as unexpected according to the SmPC, sponsor must unblind the subject before reporting it to the Danish Medicines Agency. A copy of the randomization list will be stored behind double lock at the office of the sponsor. PI is not unblinded, except in case of a medical emergency and only if PI finds it necessary to ensure the safety of the subject. PI can unblind a single subject by breaking the individual code-envelope related to the subjects blinding code. The code-envelopes will be stored together with the trial medicine at the site of the trial and will be available 24/7.
- Under section 89(2)(i) of the Danish Medicines Act, the sponsor must immediately inform the Danish Medicines Agency if any suspected unexpected and serious adverse reactions occur during the trial.
- The sponsor must ensure that all relevant information about suspected unexpected serious adverse reactions (SUSAR), which are fatal or life-threatening, is recorded and reported to the Danish Medicines Agency as soon as possible, and no later than 7 days after the sponsor is informed of such a suspected adverse reaction. No later than 8 days after the reporting, must the sponsor inform the Danish Medicines Agency of relevant follow-up information on the sponsor's and the investigator's follow-up action to the reporting. Any other suspected unexpected serious adverse reactions must be reported to the Danish Medicines Agency no later than 15 days from the time when the sponsor is informed about them. All reports must be accompanied by comments on possible consequences for the trial.
- Reporting of SUSAR is done by filling in and submitting the Danish Medicines Agency's e-form for reporting of non-commercial sponsors of suspected unexpected serious adverse reactions (SUSARs) seen in clinical trials.
- Once a year throughout the duration of the clinical trial, the sponsor must provide a list of all suspected serious adverse reactions which have occurred during the trial period and a

report on the trial subjects' safety. The list and the report must be submitted to the Danish Medicines Agency and the Ethical Committee.

- No more than 90 days after completion of a trial, the sponsor must inform the Danish Medicines Agency that the trial has been completed. As soon as possible and no later than one year after the trial has ended, the trial results must be entered in EudraCT. Subsequently, data will be published on www.clinicaltrialsregister.eu

8.6 Safety related to the COVID-19 pandemic

Because of the COVID-19 pandemic, the Danish Medicines Agency in October 2020 demanded that all clinical trials in Denmark should take precautions to reduce the risk of infection with COVID-19 for trial participants. It was therefore decided to re-schedule the 4, 8, and 16-week follow-up visits as telephone visits, to reduce traveling and contact with trial personnel. As a consequence, vital signs could only be performed at baseline and 12 weeks follow-up. As there was no reasonable suspicion that vital signs would be influenced by the trial medication, this change was deemed safe for the participants.

9.Statistics

9.1 Description of the statistical methods

Our main analysis will be calculation of between group differences in the continuous outcomes such as change scores for primary and key secondary outcomes using Repeated-Measures Analysis of Covariance (ANCOVA) procedures based on linear mixed model, which is valid under the assumption that missing data is missing at random. In an ANCOVA any potential between group differences at baseline will be adjusted for subsequently in the statistical analysis by adjusting for the level at baseline. Secondarily an analysis of number of responders in the two groups will be carried out. A responder is defined as a participant who reports a more than 15%, 30%, and 50% decrease in pain after 12 weeks of treatment with LDN. For these dichotomous outcomes logistic regression will be used to calculate relative differences between the two groups. The prespecified efficacy analyses will be based on the data for full analysis set; the intention-to-treat (ITT) population, which includes all participants that are assessed and randomized at baseline. In the case of missing data during the 12 week trial, repeated measure linear mixed models will adjust for that indirectly. In order to confirm the robustness of the findings for the primary and key secondary outcomes, sensitivity analyses will be performed to the primary analyses, including the *(i)* 'As Observed' population (assuming data were missing completely at random), *(ii)* non-responder imputation (using baseline observation carried; potentially valuable if data is not missing at random), and *(iii)* the 'Per Protocol' population.

Per protocol population will be defined as: Participants with an adherence to the treatment of at least 80%.

9.2 Trial interpretation

The trial is considered a success if the improvement of the primary outcome is significantly higher in the active group than in the placebo group, defined as the 95% confidence interval being above zero and the significance level being below 0.05. The trial is considered inconclusive if the improvement of the primary outcome is not reaching a significant level. The trial is considered negative if the improvement of the primary outcome is higher in the placebo group regardless of the significance level.

10. Direct access to sourcedata/sourcedocuments

According to the Danish executive order on GCP, informed consent from the subjects will also include consent to monitoring, auditing and/or inspection. Investigator is authorized to direct access source data/documents (including patient's files) in connection with monitoring, auditing and/or inspection by a scientific ethics committee, the Danish Medicines Agency or by health authorities in other countries.

11. Quality control and quality assurance

It is confirmed that ordinary procedures for quality control and assurance are complied with, cf. sections 3 and 4 in the Danish executive order on GCP.

12. Ethics

12.1 Ethical considerations

Approval has been obtained from The Danish Data Protection Agency. Data security will be maintained for 5 years and afterwards all data will be stored according to rules and regulations specified by the Danish Data Protection Agency.

The trial is initiated by the investigators. Neither investigators nor subjects have any economic interests in the trial.

Half of the participants will receive active treatment with LDN and half of them will receive placebo. A parallel group design was chosen to reduce bias and secure a trial with good internal validity (i.e. scientific credibility).

The participants are at risk of having side effects from the study medication. No serious adverse reactions have ever been reported during treatment with LDN. Side effects expected most likely to occur are: Headache, vivid dreams, nausea, diarrhea and abdominal pain.

Potential benefits for the participants are that they might experience reduced tenderness, reduced pain, improved sleep, improved energy and improvement in daily functioning. All participants regardless if they received active treatment or placebo will be offered treatment with LDN in an individual dosing after termination of the trial. The results from the study will be of benefit for other patients with FM.

12.2 Recruitment, information and collection of informed consent

Participants for the trial are partly recruited among patients who have been referred to treatment at a public pain center in the Southern Region of Denmark, and partly from advertising in relevant printed or internet media.

Participants recruited from the pain clinic will receive written information about the trial from their nurse or physician. For participants recruited via advertising, written information is send by e-mail. For all participants, oral information is given by telephone by the Principal Investigator. It is emphasized that participation is voluntary, and that consent can be withdrawn at any time. The participant is given a minimum of 24 hours of reflection, before informed consent is collected. Before informed consent is collected oral information about the trial is repeated. The participant is informed that she has the right to bring an assessor, when receiving oral information about the trial. It is secured that the information can be given in privacy.

13. Handling and filing of data and biological material

13.1 Handling of data

Data obtained from the participants file will be data about concomitant medication from the shared medication record and laboratory data (blood tests and ECG). No data will be obtained from the participants file, before informed consent is given.
Questionnaire data are entered directly into the eCRF in RedCap by the participants.
All other data are entered into the eCRF in RedCap by the primary investigator or the study nurse.
Later data will be transferred to a statistical program for analyzing.
5 year after termination of the study, the data will be anonymized.

13.2 Handling of biological material

Blood for a research bio bank will be collected at baseline and after 12 weeks of treatment. The purpose of the bio bank is to be able to measure a possible reduction in proinflammatory cytokines in participants receiving active treatment compared to placebo. For this purpose, 2 x 0.5 ml serum and 2 x 0.5 ml plasma is collected at baseline and after 12 weeks of treatment.
Any excess blood will be stored for 10 years. After 10 years the blood will be destructed.
The blood in the bio bank will be destructed no later than 01.01.2030.
Informed consent to perform analyzes for other research purposes are collected from all participants.

14. Financing and insurances

14.1 Insurance

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

14.2 Financing

Salary:
Salary for the primary investigator is covered by Ph.D. salary.

TAP:

Salary for study nurse (780 hours)	260.000 Dkr

Operating expenses:

Trial medication	150.000 Dkr
GCP monitoring	20.000 Dkr
Database	30.000 Dkr
Compensation to subjects for transport	300.000 Dkr
ECG, blood tests, bio bank, s-naltrexone	100.000 Dkr
Apparatus, software etc.	10.000 Dkr
Total	870.000 Dkr

Funding of operating expenses has been granted from The Danish Reumatism Association with a grant of 175.000 Dkr. The grant will be transferred to a separate research account for the project (account number: 10224731).

Funding will be applied for from other relevant public and private funds.

14.3 Compensation for subjects

Subjects that reside more than 25 kilometers away from the place of the trial, will receive compensation for expenses for transportation. The compensation fee is 1.97 Dkr per kilometer and it is tax free.

15. Publication

Information about the trial is published at ClinicalTrials.gov and EUDRACT before enrolment of the first patient.

The protocol will be published in an international peer-reviewed journal (e.g. Trials, or BMJ Open).

Results from the study is planned to be published in high impact international peer-reviewed journals. Both positive, negative, and inconclusive results will be published. All data will be anonymized.

First author will be Karin Due Bruun.

Last author will be Palle Toft.

Co-authors will be all Co-investigators that fulfill the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

16. Appendix

Appendix 1: ACR-1990 criteria (in Danish)

Appendix 1

ACR-1990 kriterier for fibromyalgi

Følgende skal være opfyldt:

Udbredte smerter (axialt + alle 4 kropskvadranter)	ja / nej
Varighed min 3 måneder	ja / nej
Ikke anden sygdom der kan forklare smerterne	ja / nej

Smerter ved 4 kg tryk på 11 ud af 18 tenderpoints:

Occiput: bilateralt ved insertion af suboccipital muskulatur
Lavt cervicalt: bilateralt ved den forreste del af det intertransversale rum ved C5-C7
Trapezius: bilateralt på midten af den øverste del
Supraspinatus: bilateralt ved udspring på scapula tæt ved den mediale kant
Anden ribben: bilateralt ved 2. costokondrale ledforbindelse, lige lateralt for leddene
Lateral epikondyl: bilateral, 2 cm distalt for epikondylerne
Gluteal: bilateralt i den øverste, laterale kvadrant af balderne i den anteriore del af muskulaturen
Trochanter major: bilateralt, lige posteriort for trochanter major prominens
Knæ: bilateralt ved den mediale fedtpude lige proksimalt for ledlinjen

	Højre	Venstre
Occiput	_____	_____
Cervicalt	_____	_____

Trapezius	_____	_____
Supraspinatus	_____	_____
2. ribben	_____	_____
Lateral epikondyl	_____	_____
Glutealt	_____	_____
Trochanter major	_____	_____
Knæ	_____	_____

Ialt _____

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