Clinical Trial Protocol

Melatonin fOr CHronic bAck pain (The MOCHA trial):
A randomized, double blind, placebo-controlled trial

In Danish:
Melatonin til kroniske rygsmerter (MOCHA studiet)

Version:	4.0 .
Date:	26.08.2024
EU CT number:	2023-503530-41-00
Clinicaltrials.gov:	NCT06476392
Approved:	December 3rd 2024

Table of contents:

1.0 General information

The trial will be carried out according to this protocol, ICH-GCP guidelines, national regulatory requirements and legislation.

Sponsor and primary investigator
Karin Due Bruun, MD, Consultant
Pain Research Group, Pain Centre
Department of Anesthesiology and Intensive Care
Odense University Hospital
Heden 7-9
5000 Odense C

GCP-monitoring
GCP-unit Odense University Hospital
Department of Clinical Biochemistry and Pharmacology
J.B. Winsløwsvej 9A, 3rd floor
5000 Odense C

Pharmacy
Glostrup Pharmacy
Hovedvejen 101
2600 Glostrup

Data management
Odense Patient data Explorative Network (OPEN)
J.B. Winsløwsvej 9A
5000 Odense C

Place for the trial:
Pain Research Group, Pain Centre
Department of Anesthesiology and Intensive Care
Odense University Hospital
Heden 7-9
5000 Odense C

1.1 Time plan

Approval from authorities:	14.03.2024
Expected first act of recruitment:	01.08.2024
Expected start of inclusion:	01.10.2024
Expected end of inclusion:	31.08.2026
Expected end of follow-up:	01.11.2026
Expected submission of papers:	01.05.2027

1.2 Abbreviations

AASM = American Academy of Sleep Medicine
AE = Adverse events
ALAT = Alanine-aminotransefase
AR = Adverse reaction
CTCAE = Common Terminology Criteria for Adverse Events
E-CRF = Electronic case report form
EEG = Electroencephalography
GCP = Good Clinical Practice
GFR = Glomerular-filtration-rate
GPE = Global Perceived Effect
hCG = Human chorionic gonadotropin
IrOx = Iridium oxide
ISI = Insomnia Severity Index
N1 = Non-rapid eye movement stage 1
N2 = Non-rapid eye movement stage 2
N3 = Non-rapid eye movement stage 3
NSAID = Non-steroidal anti-inflammatory drug
OPEN = Odense Patient data Explorative Network
PPT = Pain Pressure Threshold
PROM = Patient Reported Outcome Measure
PROMIS-10 = Patient-Reported Outcomes Measurement Information System
REM = Rapid eye movement
RMQ = Roland Morris Disability Questionnaire
SAE = Serious adverse event
SAP = Statistical analysis plan
SAR = Serious adverse reaction
SE = Sleep efficiency
SmPC = Summary of Product Characteristics
SOL = Sleep onset latency
SPT = Sleep period time
SUSAR = Serious unexpected suspected adverse reactions
TST = Time from sleep onset until final awakening
WASO = Wake after sleep onset
WHO = World Health Organization

2.0 Background

2.1 Trial background

According to the World Health Organization (WHO) Global Burden of Disease study, back pain is one of the conditions impacting disability the most worldwide.[1,2] Pain medication use in patients with chronic back pain is substantial, but the efficacy of commonly used analgesics such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants and opioids compared with placebo are modest, with effects typically less than 10 points on a 0-100 pain scale [3-5]. Importantly, these analgesics are not harmless due to gastrointestinal and cardiovascular side-effects (NSAIDs) and risk of dependency and addiction (opioids) [3-5]. This often leave general practitioners without good treatment options for many patients with chronic low back pain.

More than half of patients with chronic back pain also have sleep problems (i.e. insomnia),[6,7] which negatively affect daily function, general health and quality of life. Research suggest that insomnia has negative effects on pain processing, and although the relationship between pain and insomnia is bi-directional, insomnia is considered to be a stronger predictor of pain than pain for the development of insomnia.[8,9]

Melatonin is a widely available drug worldwide, and well known for its use in people with sleep disorders and jetlag. Melatonin is a naturally occurring hormone excreted by the pineal gland that is part of regulating the circadian rhythm (sleep-wake patterns).[10] Unlike commonly used drugs to treat back pain, the safety profile of melatonin is favorable with no adverse events of major clinical significance reported in the treatment of sleep disorders.[11,12] In recent years, some preliminary studies have showed a promising effect of Melatonin for treatments of pain (i.e. as pain medication). A meta-analysis reported an effect size of 0.65 (95%CI 0.34 to 0.96) of Melatonin (doses ranging between 3-10 mg before sleep) compared with placebo in reducing pain in patients with non-musculoskeletal chronic pain (e.g. migraine, irritable bowel syndrome, burning mouth syndrome), suggesting that Melatonin could potentially also be a valid treatment option for chronic musculoskeletal pain patients.[13]

Given the effect of Melatonin on sleep and the potential effect of Melatonin on pain,[14] we also plan to explore the potential mediating effect of Melatonin on pain through improvement of sleep.

2.2 Summary of results from previous trial on Melatonin for fibromyalgia and chronic back pain

Based on previous systematic reviews,[15,16] we have identified 4 studies on Melatonin for patients with fibromyalgia and chronic musculoskeletal pain. However, most of the studies had no placebo comparator.

One Russian study,[15] including 178 patients aged 40–65 years with chronic back pain (>3 months pain) had 6 treatment groups, that were analyzed in 3 comparisons. The effect of Melaxen® 3 mg (Melatonin) as an add on treatment to Artra® (Unipharm Inc.; combination of 500mg glucosamine hydrochloride and 500mg chondroitin sulfate) and/or diclofenac (NSAID) was explored. In comparison 1, treatment with Artra one tablet twice daily for 1 month, followed by Artra one tablet once daily for 2 months (n=29) was compared to the same treatment regime plus Melaxen 3 mg 30-40 minutes before bedtime (n=31). In comparison 2, treatment with Artra one tablet twice daily plus diclofenac 25 mg 2-3 times a day (n=30) was compared to the same treatment regime plus Melaxen 3mg 30-40 min before sleep (n=30). In comparison 3, treatment with diclofenac 25 mg three times a day (n=29) was compared to the same treatment regimen plus Melaxen 3mg 30-40 min before sleep (n=29).

Overall, the results favored groups receiving Melaxen (Melotonin) with better results regarding pain, function, anxiety and sleep.

An Iraqi study,[17] examined the effect of Melatonin (3 mg/day or 5 mg/day) in addition to an antidepressant (Fluoxetine 20 mg/day) over 8 weeks. The study included 101 patients (18-65 years) with fibromyalgia according to the American College of Rheumatology (ACR) 1990 classification criteria. Participants were randomized to one of 4 groups: 1) Fluoxetine 20 mg/day; 2) 5mg/day Melatonin; 3) 3mg/ day Melatonin + Fluoxetine 20 mg/day; 4) 5mg/ day Melatonin + Fluoxetine 20 mg/day. Melatonin groups experienced the largest within group changes in pain, but no between group statistical analysis was performed hampering the interpretation of these results.

A Brazilian study,[14] compared 3 groups over six weeks. The study included 63 patients (mean age about 50 years) with fibromyalgia according to the ACR 1990 criteria. Group 1 received 25 mg Amitriptyline (an antidepressant) + placebo; group 2 had 10 mg Melatonin + placebo; and group 3 had 25 mg Amitriptyline + 10 mg Melatonin. Both groups receiving Melatonin had significantly larger reductions in pain compared to the Amitriptyline alone group.

Finally, a Spanish study,[18] including patients with fibromyalgia (patients aged 40-60 years) investigated the dose-response relationship of 10-day periods with progressively higher of doses of Melatonin (3, 6, 9, 12 and 15mg Melatonin), separated by 10-day placebo wash-out periods on several outcomes, including pain. Doses of 9, 12 and 15mg Melatonin all resulted in decreased pain compared to baseline and the initial placebo period, this was not observed for 3 and 6mg doses.

The above-mentioned previous studies of melatonin had a treatment duration varying from 10 days to 8 weeks. The study with 10 days duration was a dose-response study, whereas the three efficacy studies had a treatment duration varying from 4 to 8 weeks. We have chosen 6 weeks treatment as it corresponds to the average treatment duration of the previous RCT studies. Furthermore, we want to ensure that the treatment duration is long enough to potentially improve sleep quality, so we can explore whether the pain relieving effect of Melatonin is mediated by an improvement of sleep.

2.3 Background information about Melatonin

Melatonin is a naturally occurring hormone excreted by the pineal gland and play a role in regulating the circadian rhythm (sleep-wake patterns) [10]. Melatonin is primarily marketed for sleep disorders and jetlag. In many countries, Melatonin is an over-the-counter drug, but require prescription in Denmark. In Denmark, the indications for prescription are: 1) short term treatment of insomnia/poor sleep quality in patients older than 55 years; 2) short term treatment of jetlag in adults; and 3) insomnia in children/adolescents with autism and/or Smith-Magenis syndrome.[19] The recommended dose is between 2 and 10 mg depending on the indication. In this trial, we will test a dose of 10 mg of oral Melatonin for off label use to treat pain in patients with chronic back pain (with and without insomnia).

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

Risks:

For patients with sleep disorders and insomnia, Melatonin has been shown to be well-tolerated in clinical studies, with no evidence of serious adverse events.[11,12] Known side effects of Melatonin is listed in the Summary of Product Characteristics (SmPC) below. In this study a dose of 10 mg will be used, and the risk of serious adverse events when using this dose for treating pain is considered minimal.

Benefits:
The potential benefit for the participants is a reduction in pain intensity, and improved sleep for those patients who suffer from insomnia in addition to chronic back pain. The results from this study has the potential to improve treatment for future patients with chronic low back pain.

SmPC for Melatonin (ATC-code N05CH01):
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)

Table 1

MedDRA system organ class	
Infections and infestations *Rare*	Herpes zoster
Blood and lymphatic system disorders *Rare*	Leukopenia, thrombocytopenia
Immune system disorders *Not known*	Hyper-sensitivity reaction
Metabolism and nutrition disorder *Rare*	Hypertriglyceridaemia, hypocalcaemia, hyponatraemia
Not known	Hyperglycemia
Psychiatric disorders *Uncommon*	Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety
Rare	Mood altered, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, libido increased, depressed mood, depression
Nervous system disorders	

Common	Headache, somnolence
Uncommon	Migraine, lethargy, psychomotor hyperactivity, dizziness
Rare	Syncope, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia
Eye disorders *Rare*	 Visual acuity reduced, vision blurred, lacrimation increased
Ear and labyrinth disorders *Rare*	 Vertigo positional, vertigo
Cardiac disorders *Rare*	 Angina pectoris, palpitations
Vascular disorders *Uncommon*	 Hypertension
Rare	Hot flush
Gastrointestinal disorders *Uncommon*	 Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, nausea
Rare	Gastro-oesophageal reflux disease, gastrointestinal disorder, oral mucosal blistering, tongue ulceration, gastrointestinal upset, vomiting, bowel sounds abnormal, flatulence, salivary hypersecretion, halitosis, abdominal discomfort, gastric disorder, gastritis
Hepatobiliary disorders *Uncommon*	 Hyperbilirubinaemia

Skin and subcutaneous tissue disorders *Uncommon*	Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin
Rare	Eczema, erythema, hand dermatitis, psoriasis, rash generalized, rash pruritic, nail disorder
Not known	Angioedema, oedema of mouth, tongue oedema
Musculoskeletal and connective tissue disorders *Uncommon*	Pain in extremity
Rare	Arthritis, muscle spasms, neck pain, night cramps
Renal and urinary disorders *Uncommon*	Glycosuria, proteinuria
Rare	Polyuria, haematuria, nocturia
Reproductive system and breast disorders *Uncommon*	Menopausal symptoms
Rare	Priapism, prostatitis
Not known	Galactorrhoea
General disorders and administration site conditions *Uncommon*	Asthenia, chest pain
Rare	Fatigue, pain, thirst
Investigations *Uncommon*	Liver function test abnormal, weight increased
Rare	Hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal

2.5 Description and justification for dose, dose regimen and treatment period

Dosages in previous identified trials evaluating Melatonin for fibromyalgia and chronic back pain have ranged between 3-15mg for 10-84 days.[14,15,17,18] One of these trials[18] including fibromyalgia patients (n=97) investigated the dose-response relationship (3, 6, 9, 12 and 15mg Melatonin) of 10-day periods of Melatonin treatment separated by 10-day placebo wash-out periods. Doses of 9, 12 and 15mg Melatonin resulted in decreased pain compared to baseline and the initial placebo period, this was not observed for 3 and 6mg doses. Thus, for this trial we will administer a dose of 10mg Melatonin/day. The reason for choosing 10mg instead of 9mg is to reduce future burden on patients. Based on data from two reviews on the safety of higher doses of Melatonin, the use of 10 mg for a longer duration has not been associated with an increased frequency of SAE's across a range of different clinical conditions.[20,21] In Denmark, 3 and 5mg tablets are commercially available, choosing a dose of 5mg will reduce the number of tablets to be taken from 3 to 2 compared with a 9mg dose (i.e. 3 x 3mg tablets/day).
The study medication (incl. placebo) will be prepared by Glostrup Pharmacy to ensure blinding of the study medication.

The intervention group will receive two 5mg Melatonin tablets to be taken 30 min. before bedtime for 6 weeks. The control group will receive placebo tablets to be taken in the same manner, as the intervention group. In both groups, continued but not new co-interventions (e.g. pain medication use [such as paracetamol and NSAIDs], exercise therapy, manual therapy etc.) are allowed. This will be monitored by self-report questionnaire.

2.6 Description of study population

We will include patients aged 18-64 years with chronic back pain with and without insomnia in this trial. For specific in- and exclusion criteria please refer to section 5.2 and 5.3.

3. Study aim

3.1 Hypothesis

Treatment with 10mg Melatonin will be superior in reducing pain intensity in chronic back pain patients compared with placebo.

3.2 Aims and objectives

The aim of this randomized double-blind placebo controlled clinical superiority trial is to investigate if daily treatment with Melatonin 10 mg once daily before bedtime for 6 weeks is superior compared with placebo in improving pain intensity assessed at 6 weeks after treatment initiation in patients with chronic back pain.

The primary efficacy objective will be to compare the effect of the drug Melatonin, relative to placebo, on difference in change in pain intensity (i.e. average pain intensity past 7 days) measured on a 0-10 NRS scale, from baseline to 6 weeks in patients with chronic back pain.

Our secondary efficacy objectives will be to compare the effect of drug Melatonin, relative to placebo, on 1) pain-related disability, 2) Global Perceived Effect (GPE), 3) insomnia, 4) health-related quality of life, and 5) pain sensitivity. Furthermore, trajectory (0 to 6 weeks) and responder indices from baseline to 6 weeks will be compared between the treatment groups for the primary outcome.

Explorative objectives are to investigate sleep patterns as well as effect-modification of presence/absence of comorbid insomnia.

4. Study plan

4.1 Study design

In this phase III trial we intend to investigate the efficacy of Melatonin for reducing pain intensity in patients with chronic back pain. To achieve the goal of testing efficacy, we will perform a randomized placebo controlled double blind clinical superiority trial. The study will include patients with chronic back pain with and without insomnia. Patients will be randomized to treatment with Melatonin or placebo (1:1 allocation ratio, random block size allocation), by a data manager outside the project. The data manager will prepare the randomization list in RedCap, and Glostrup Pharmacy will package the study medication according to this randomization list.

Patients responding to trial advertisements will after an initial phone screening be invited to a clinical visit (visit 1) for patient information, assessment of eligibility and signing of informed consent. The study related examinations and procedures at visit 1 A will only be made if the participants sign the informed consent at the beginning of visit 1A. If the participants want to think whether to participate, they will at least have 24 hours consideration period, and the examinations listed at visit 1A will first be made, when the informed consent is signed.
Patients consenting to participate and matching the eligibility criteria will be invited for a 2nd clinical visit (visit 2), where final decision on inclusion will be made. Included patients will then have baseline assessments performed, be randomized and study medication will be extradited. The trial period is 6 weeks (safety assessment in week 3 – phone), and with an end of follow-up phone call to patients for safety after 8 weeks from study start (Figure 1).

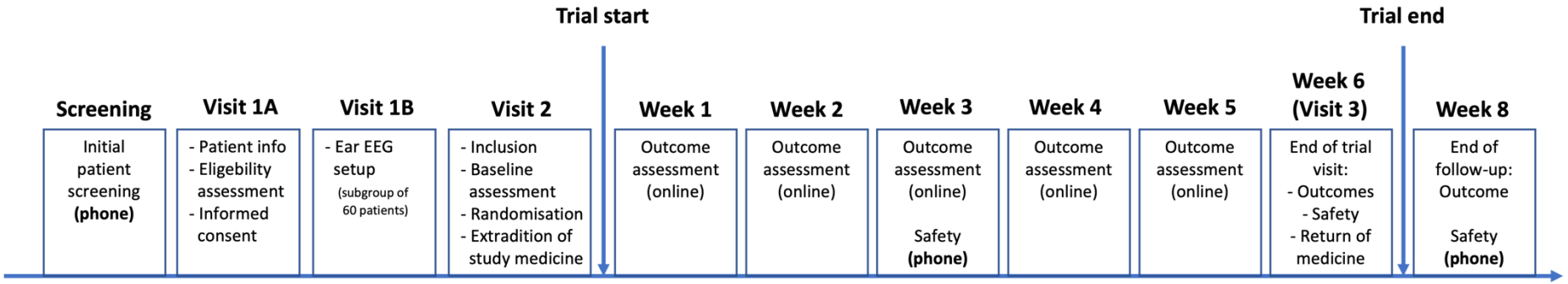

Figure 1: Study overview.

4.2 Trial procedures and study visits

Detailed description of procedures and study visits:

Initial patient screening (phone):

- Initial eligibility criteria (see section 5.2 and 5.3 for in-/exclusion criteria) that can be assessed over the phone
- Brief information about the study
- Appointment for eligibility visit 1 (if potentially eligible after initial screening)

Eligibility assessment (physical visit 1A):

- Additional patient information and time for questions
- Informed consent
- Medical history
- Vital signs (blood pressure, heartrate, weight, height)
- Urine test (Human chorionic gonadotropin [hCG] for pregnancy)
- Blood sample (Alanine-aminotransefase [ALAT], creatinine, Glomerular-filtration-rate [GFR])
- Ear measurement for individual molding of ear electroencephalography (EEG) device (subgroup of 60 patients) – see section 7.2.3 for specific procedures on ear EEG.

Ear EEG setup (physical visit 1B – subgroup of 60 patients):

- Instruction and handing out ear EEG to patients
- Start 7-day adaption period for sleeping with ear EEG (2 days with; 1 day without; 2 days with; 2 days without)
- After 7-day adaptation period – EEG sleep baseline assessment (5 out of next 7 days) (there must be 14 days between physical visit 1B and physical visit 2 to allow for adaptation period and baseline EEG measurement)

Inclusion, baseline testing and randomization (physical visit 2):

- Urine test (hCG for pregnancy)
- Vital signs (blood pressure, heartrate, weight, height)
- Study inclusion
- Primary outcome
- All other PROMs
- PPT
- Randomization
- Handing out study medication

Outcome assessment (Week 1):

- Primary outcome

Outcome assessment (Week 2):

- Primary outcome

Outcome and safety assessment (Week 3 – phone):

- Primary outcome
- ISI
- Urine test (hCG for pregnancy) – at home
- Questionnaire about adverse events
- Phone call for adverse events and check of pregnancy test done

- Remind 60 patient EEG subgroup to start follow-up EEG sleep assessment in week 4

Outcome assessment (Week 4):
- Primary outcome
- EEG sleep follow-up assessment (5 out of next 7 days) – subgroup of 60 patients

Outcome assessment (Week 5):
- Primary outcome

Outcome assessment (Week 6 – physical visit 3):
- Primary outcome
- All other PROMs
- PPT
- Adverse events
- Return ear EEG device (60 patient subgroup)
- Return left over study medication

Outcome assessment (Week 8 – phone):
- Primary outcome
- ISI
- Adverse events
- Urine test (hCG for pregnancy) – at home

4.3 Primary and secondary outcomes

Primary outcome:
- Average back pain intensity during the past 7 days. Difference in change between treatment groups (Melatonin vs. placebo) from baseline to 6 weeks. Average pain intensity during past 7 days will be assessed on a 0-10 Numeric Rating Scale (NRS) (ranging from 'no pain to 'worst imaginable pain').[22] The participants will be recommended to respond to the question about their average pain intensity during the last week at the same time of the day as they will take the study medicine (before bedtime). In that way the primary endpoint will be assessed at the same time consistently throughout the trial.

Secondary outcomes:
- Trajectory of weekly (at 0, 1, 2, 3, 4, 5 and 6 weeks) NRS back pain intensity scores (primary outcome) from baseline to 6 weeks.[22]Number of patients with more than 30% improvement in the primary outcome from baseline to 6 weeks (Number of responders are calculated for both the Melatonin and the placebo group).
- Number of patients with more than 50% improvement in the primary outcome from baseline to 6 weeks (Number of responders are calculated for both the Melatonin and the placebo group).
- Back pain related disability. Difference in change between treatment groups (Melatonin vs. placebo) from baseline to 6 weeks. Back pain related disability will be assessed using the Roland Morris Disability Questionnaire (RMQ).[23,24] RMQ is a 23-item questionnaire (RMQ) developed to assess functional limitation and disability among patients with low back pain. The RMQ 23-item version will be used because 1) it has been cross-culturally validated in Danish (the original RMQ 24-item version

has not), 2) the psychometric properties of the 23 vs 24 item RMQ have been shown to be similar.[25,26] Each of the 23 items is yes/no (scored as 1 and 0 points respectively) with the scale ranging from 0 (no disability) to 23 (extremely severe disability).

- Global Perceived Effect (GPE). Assessment of overall change in back pain from baseline to 6 weeks. Participants will be asked at 6 weeks: 'How is your back pain now compared to when you entered this study', with 5 response options (much worse, worse, almost the same/unchanged, improved, much improved).[27]
- Physical and mental health will be assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS-10) Global Health questionnaire version 1.2.[28] Difference in change in physical and mental health scores between treatment groups (Melatonin vs. placebo) from baseline to 6 weeks. PROMIS-10 consist of 10 questions concerning different aspects of global health. The first 9 questions are score on a Likert scale with 5 response options, and the last question is asking about pain using a 0-10 numeric rating scale.
- Insomnia symptoms. Difference in change between treatment groups (Melatonin vs. placebo) from baseline to 6 weeks. Insomnia will be assessed with the Insomnia Severity Index (ISI), which is a brief 7 item patient-reported instrument with a score ranging from 0-28 (0=best;28=worst), insomnia will be defined according to described cut-offs.[29,30]
- Pain sensitivity (i.e. pressure pain threshold). The primary aim of this trial is to investigate if Melatonin is superior compared with placebo in improving patient-reported pain. To enable us to report the potential effect on similar yet different domain of pain (i.e. objectively assessed pain sensitivity), we have included an outome measure of pain sensitivity. Difference in change between treatment groups (Melatonin vs. placebo) from baseline to 6 weeks. Pressure pain threshold is assessed using a handheld algometer.[31,32] Pressure pain thresholds will be assessed locally at the right erector spinae muscle (3 cm from the fourth lumbar spinous process) and at the left upper trapezius muscle (10 cm horizontally from the acromion in direct line with the seventh cervical spinous process).

Exploratory outcomes:

- Physiological sleep (subgroup of 60 patients). Difference in change in sleep metrics between treatment groups (Melatonin [n=30] vs. placebo [n=30]) from baseline to 4 weeks. The following sleep metrics will be assessed using ear EEG: sleep period time (SPT); time from sleep onset until final awakening (TST); sleep efficiency (SE) which is the ratio of TST to time in bed / 100%; sleep onset latency (SOL); wake after sleep onset (WASO), wake time within the SPT. The following sleep architecture variables will be used: REM sleep latency, time from sleep onset until first epoch of REM stage sleep; amount of wake and stage N1, N2, N3, and R sleep as a percentage of SPT; number of awakenings within TST; arousal index which is number of arousals per hour.

Data collected during screening:

- Demographic data (sex, smoking, alcohol use, physical activity level, work status, civil status, etc.)
- Concomitant medicine use
- Serum levels of ALAT, creatinine, GFR
- Vital signs (Blood pressure, heart rate, weight, height)
- Urine – hCG (i.e. test for pregnancy)

Table 2: Detailed overview of timing of outcomes and assessments.

	Screening (Phone)	Eligibility assessment (Visit 1A)	Ear EEG setup (Visit 1B)	Inclusion & baseline assessment (Visit 2)	Week 1	Week 2	Week 3 (Phone)	Week 4	Week 5	Week 6 (Visit 3)	Week 8 (Phone)
Eligibility assessment	X	X									
Medical history		X									
Urine test		X		X			X			X	
Blood test		X									
Informed consent		X		X							
Vital signs including weight and height		X		X						X	
NRS pain				X	X	X	X	X	X	X	X
RMQ				X						X	
GPE										X	
ISI				X			X			X	X
PROMIS-10				X						X	
Pain sensitivity				X						X	
Sleep pattern (EEG) (60 patients)		X	X	X				X			
Adverse events				X			X			X	X

** The study related examinations and procedure at visit 1 A will only be made if the participants sign the informed consent at the beginning of visit 1A. If the participants want to think whether to participate, then the examinations listed at visit 1A will be made at Visit 2.*

4.4 Sample size estimation

We aim to be able to detect a difference in treatment effect between groups of 1 point on a 0-10 NRS scale (similar effect as NSAIDs for acute and chronic low back pain).[4,33] With 80% power and an alpha-level of 0.05 (assuming a SD of 2.5 on the change score), 100 patients have to be included in each group when using a t-test for the analysis. The approach to use baseline values as covariates instead of change scores implies a further gain in power. Drop outs may decrease the power, but due to using a mixed model for analysis, they will still contribute information. To take a potential loss in power into account, the sample size is increased by 10%, i.e. we aim at a total sample size of 220 patients.

4.5 Measures for reduction in bias

Participating patients, investigators, outcome assessors and statistical analysts are all blinded to treatment allocation. All patient reported data will be filled in by the patient via an online questionnaire using REDCap. An assessor blinded to study treatment will perform all protocol specific objective outcome assessments at baseline and 6 weeks follow-up. Unblinding will first take place after the primary analysis of the data has taken place.

A data manager, otherwise, not involved in the study, will prepare the randomization list, using a computerized algorithm in REDCap. The randomization list will be sent to Glostrup Pharmacy, 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 trial medicine will be shipped together with individual code-envelopes for every blinding code to the place of trial, and trial site will be responsible for reception control. The code-envelopes will be stored at the department of Anesthesiology and Intensive care at Odense university hospital (OUH) behind double lock and it can be accessed 24/7.

Sponsor/PI is not unblinded, except in case of a medical emergency and only if PI/ Sponsor finds it necessary to ensure the safety of the subject. The investigator will be able to unblind a single participant if medically necessary at all times of the day, without delay or previous contact to the sponsor. A single subject can be unblinded by breaking the code-envelope related to the subjects blinding code. If a code-envelope is opened, it is stored in the trial master file.

4.6 Description of the study treatment

After inclusion participants are randomized according to the abovementioned procedure to receive either Melatonin (10 mg/day) or placebo for 6 weeks.
The Glostrup Pharmacy will purchase the active melatonin medicine and manufacture the identical appearing placebo tablets. The trial medicine will be labeled with blinding codes according to the randomization list by Glostrup Pharmacy. Before dispensing the trial medication, the ID-number of the study participant will be written on the medicine cans. The trial medicine is to be taken once daily in the evening, 30 min. before going to sleep.

If a participant experiences an adverse event deemed related to the study medication of grade 2 or higher according to CTCAE version 5.0 the dose will be reduced to 5 mg/day.

4.7 Description of expected time frame for the individual patient

The time frame for the intervention is 6 weeks, with an end of study follow-up phone call for safety at 8 weeks.

4.8 Rules for termination of the study

The study will be terminated when all recruited participants have completed their final follow-up (last patient – last visit). The study will be terminated prematurely, if unforeseen issues regarding the safety of the study drug should occur.

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

The study medicine and the placebo tablets will be packaged at Glostrup Pharmacy. The study medicine will be delivered together with code-envelopes to the place of the trial (The Pain Centre, Odense University Hospital), 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.

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 6 weeks. Trial medication is handed out at baseline (week 0). At the end of the intervention phase, empty medicine-cans will be returned, and any non-ingested medicine will be counted by a trained employer at the Pain Center OUH. Participants will be asked if they lost any of the tablets. Both number of returned tablets and number of lost tablets will be recorded
To be considered adherend to the protocol it requires at least 80 % adherence to the treatment. The study medication and placebo will be counted at study end visit. If the study medicine has been reduced during the study period due to adverse events, this will be taken into account, when calculating the adherence of the study medication. The remaining study medicine and the placebo tablets will be destroyed at the Hospital pharmacy Funen.

4.10 Source data

Source data that appears from the electronic case report form (E-CRF) are demographic data, questionnaire data, concomitant medicine, adverse events (AE) and adverse reactions (AR) and data from assessments of Pressure pain thresholds.
Source data that appears from the patient´s medical record is laboratory data (blood tests).
Source data from the EEG assessments will be stored in an online Sharepoint folder.
In case of system break down, all data will be collected in a paper version similar to the E-CRF version. This data will be entered into the E-CRF as soon as the break down has been resolved. Any source data in paper format will be archived in the trial master file.

5. Selection and withdrawal of participants

5.1 Selection and screening of patients

Based on the 2021 National Health Profile more than 950.000 people suffer from back pain in Denmark,[34] and it is the most common reason to visit the general practitioner.[35] Therefore, we will use a recruitment strategy with advertisements and social media campaigns. We have previously used this method with success for recruitment of chronic pain patients in other trials.[36] Participants that respond to advertisements will receive written information material about the trial using E-boks, which is a digital system used for all communication between Danish authorities and citizens. They will also be contacted by telephone a few days after receiving the written information. During the telephone call additional oral information will be given, patients will be able to ask questions and patients will respond to initial screening

questions for eligibility. Participants interested in participating in the trial and fulfilling the initial eligibility criteria will be invited to a screening interview and eligibility examination at the Pain Center at Odense University Hospital (visit 1). Participants fulfilling all eligibility criteria and signing informed consent will be invited to an additional visit (visit 2 – Pain Center, Odense University Hospital). As eligibility assessment require blood testing with some delay in response, the final decision on inclusion of patients will be made at visit 2, followed by baseline testing, randomization, and extradition of study medication. In case, results from blood samples violate the eligibility criteria, patients will be contacted by phone to cancel visit 2 and informing them that they are not eligible for the study.

5.2 Inclusion criteria

To be eligible for the trial patients must fulfill the following inclusion criteria:

- Age 18 to 64 years
- Understand and write Danish
- Back pain for 3 months or longer
- Back pain must be present on 'most days' or 'every day' within the past 3 months (will be checked by the question: 'In the past 3 months, how often did you have back pain? – response options: 'never'; 'some days'; 'most days'; 'every day')
- Back pain must limit life or work activities on 'some days', 'most days', or 'every day' within the past 3 months. (will be checked by the question: 'In the past 3 months, how often did your back pain limit your life or work activities? – response options: 'never'; 'some days'; 'most days'; 'every day')
- Average pain intensity of ≥4 on 0-10 Numeric Rating Scale [NRS] in the past 7 days (ranging from 'no pain' to 'worst imaginable pain').
- All fertile women must use safe contraception (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 contraception. 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 (reported by the participant).

5.3 Exclusion criteria

Patients be excluded based on the following exclusion criteria:

- Known abuse of alcohol or other substances
- Self-selected non-user of e-boks
- Opioid use (reported by participant)
- Known malignancies within past 6 months (reported by participant)
- Known fractures within past 4 months (reported by participant)
- Known lumbar radiculopathy (reported by participant)
- Known spinal stenosis (reported by participant)
- psychiatric disorders and/or psychotic symptoms evaluated by the investigator (reported by participant)
- Suicide and self-damage thoughts (reported by participant)
- Inflammatory/autoimmune arthritis (reported by participant)
- For the EEG subgroup:
    - If the anatomy of the outer ear making it impossible to do ear EEG monitoring
    - If there have a perforation of the tympanic membrane (eardrum)
    - If they have an ear tube in the tympanic membrane

    - If their ear piercings that are not compatible with ear EEG.
    - If they use anticoagulants

- Patients with contraindications to Melatonin according to the Danish Medicines Agencys approved product information:
    - Moderate to severe kidney insufficiency (GFR < 30 mL/min)
    - Moderate to severe liver insufficiency (ALAT must not be elevated more than 3-fold over highest reference level)
    - Auto-immune diseases
    - Epilepsy
    - Warfarin use
    - Benzodiazipin use (including hypnotics)
    - Fluvoxamin use (Ciprofloxacin, Norfloxacin)
    - Calcium antagonist use (Verapamil, Nifedepin)
    - Pregnancy or pregnancy-wish or breastfeeding (a negative pregnancy test has to be available for all fertile female patients at baseline)
    - Intolerance to melatonin

5.4 Procedures for withdrawal

A participant will be withdrawn from the study medication:

1) In case of a 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) If the participant during the trials wants to cease the treatment, the participant is withdrawn from the study medication.
3) If the participant during the trial wants withdraw from the study, the participant is withdrawn from the study and will not be contacted for further assessments.

All participants that are withdrawn from the study medication will be encouraged to complete all visits as scheduled. Prematurely discontinued participants will be followed up weekly by telephone until any adverse events have ceased or are stable. Participants that are withdrawn from the treatment will not be replaced, and will be included in the intention-to-treat population. According to our sample size calculation, we will include participants enough to tolerate a drop-out rate of up to 20%. Both intention-to-treat and per protocol analysis will be performed and compared to assess the robustness of the primary analysis.
If changes in the patient's other pain medication occur during the trial, this will be considered a protocol violation, and the participant will not be included in the Per Protocol Population.

6. Patient treatment

6.1 Detailed description of the study treatment

The planned trial period with study treatment is scheduled to 6 weeks (42 days). Patients will receive either 10 mg Melatonin (2 x 5 mg tablets) or placebo (2 tablets looking identical to the study medication) to be taken once daily approximately 30 min before bedtime during all days in the study period. The study medication is not to be taken within 2 hours of a meal.

To take into account that the final follow-up visit (visit 3) may not be possible to schedule for all patients at day 42 and that the effect of Melatonin is transient, all study participants will receive 100 tables of the study medication (Melatonin or placebo) corresponding to 50 days

of treatments. Patients will be instructed to continue treatment until the end of trial visit (visit 3).

If a participant experiences an adverse event deemed related to the study medication of grade 2 or higher according to CTCAE version 5.0 the dose will be reduced to 5 mg/day.

Special considerations in relation to intake of study medication to convey to patients:

- NSAIDs should not be used by study participants in the evening (may reduce the level of endogenous melatonin)
- Betablockers should be used in the morning as it may suppress endogenous melatonin
- Individuals with impaired glucose tolerance or diabetes should not take the study medication within 3 hours of a meal (instead of 2 hours)

6.2 Off label use

Melatonin is primarily marketed for sleep disorders and jetlag. In many countries Melatonin is an over-the-counter drug, but require prescription in Denmark. In Denmark, the indications for prescription are: 1) short term treatment of insomnia/poor sleep quality in patients older than 55 years; 2) short term treatment of jetlag in adults; and 3) insomnia in children/adolescents with autism and/or Smith-Magenis syndrome.[19]

In this trial the use of melatonin will be 'off label use' to treat pain in patients with chronic back pain.

6.4 Rules for concomitant medication/treatment during the trial

In the trial we will allow continued, but not new co-interventions (e.g. pain medication use, exercise therapy, manual treatment etc.). This will be monitored by the shared electronic medications record and by questionnaire.

6.5 Measures to promote compliance

Participants will receive a weekly 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 patients after termination of the study

Treatment of patients will terminate after 6 weeks (visit 3), there will be no additional treatment with the study medication after the 6 weeks (visit 3). As recruitment is conducted through open sources (i.e. social media and advertisements) and not through a clinical pathway patients that still have back pain after the study period will be recommended to contact their own general practitioner. The general practitioner will then facilitate treatment according to general guidelines and standard procedures for treatment of patients with back pain in primary care.

7. Outcomes

7.1 Study outcome measures

For a detailed description of the study outcomes please refer to section 4.3

Primary outcome:

- Pain intensity - NRS pain (average in the past 7 days)

Secondary outcomes:
- Back pain related disability - Roland Morris Disability Questionnaire (RMQ)
- Global Perceived Effect (GPE)
- Physical and mental health - Patient-Reported Outcomes Measurement Information System (PROMIS-10) Global Health questionnaire v. 1.2.
- Insomnia symptoms – Insomnia Severity Index (ISI)
- Pain sensitivity –pressure pain threshold (PPT)

Exploratory outcomes:
- Physiological sleep metrics – ear EEG

7.2 Description of specific assessment procedures

7.2.1 Patient-reported outcomes:
All patient-reported outcomes will be collected using an online questionnaire administered through REDCap, which ensure data logging and comply with all demands from the Danish Data Protection Agency regarding data security. For timing of collection of patient-reported outcomes please refer to section 4.3.

7.2.2 Pressure pain thresholds (PPT)
PPTs are assessed using a handheld algometer.[31,32] Handheld pressure algometry with a manually applied standardized pressure stimulation to assess pain sensitivity of deep structures is a reliable method that is extensively used and validated[32,37]. PPTs will be assessed locally at the right erector spinae muscle (3 cm from the fourth lumbar spinous rocess) and at the left upper trapezius muscle (10 cm horizontally from the acromion in direct line with the seventh cervical spinous process) using a handheld pressure algometer (Somedic Sales AB, Norra Mellby, Sweden) with a stimulation area of 1 cm2, and a pressure rate of 30 kPa/s. Patients are instructed to press a button when the pressure is perceived as the first sensation of minimal pain. Two assessments with 20-second intervals between assessments are completed for each site and the average at each site is used for analysis. For timing of assessment of PPT please refer to section 4.3.

7.2.3 Physiological sleep metrics (subgroup of 60 patients)
After recruitment of the first 100 patients, 60 patients will be selected for objective assessment of sleep. Before inclusion of the first patient in this sub-study we will notify VMK about the ear EEG sub-study, which is a clinical investigation of medical devices under MDR article 82. This sub-study application is expected to be submitted to VMK in 2025, when it has been finally clarified whether the ear-EEG equipment that will be used in the sub-study has achieved CE marking or not. Assessment of changes in sleep metrics will be performed during two 5 of 7-day periods. One period at baseline prior to initiation of study treatment (between visit 1B and visit 2) and one period in week 4. The assessment will be performed using an ear-EEG research solution (T&W Engineering A/S, Lynge, Denmark) that is custom-fitted for each individual patient. The Recorder and headset are both a low-risk class I medical device in EU. T&W Engineering provides and supports the solution throughout the study period, including ongoing firmware updates to ensure data quality. Components that break during the study will be replaced. All Recorders and Headsets will be returned to T&W Engineering when they are no longer needed, breaks, or need firmware update. Prior to the actual assessment each individual patient will have a custom-fit earplug

moulded, which will hold the EEG electrodes. Furthermore, patients will be instructed in the use of the system. Previous studies have demonstrated the feasibility of measuring ear EEG in patients own home and shown that ear-EEG compares to conventional scalp-EEG (i.e. used in polysomnography assessment of sleep) with similar performance.[38,39] Sleep variables will be derived from the EEG assessments as recommended by the American Academy of Sleep Medicine (AASM).[40] The intended purpose of the ear-EEG solution is to acquire, record, and transmit electrical brain activity (EEG) of patients 18 years and older. The solution is composed of a Recorder and a Headset. The Recorder is a battery-powered logging device for multiple use. The Headset is an electrode array intended for single patient - multiple use, to acquire electrical activity of the brain (EEG) using the Recorder. The Headset is composed of two customized earpieces each containing 3 embedded dry electrodes. The electrodes are placed inside the ear canal and in the concha of the ear. All investigators will be trained in the use of the ear-EEG solution prior to initiation of the study. This includes customization of ear pieces, mounting of earpieces, and setting up and downloading data from the ear-EEG solution. The earpieces are labelled with lot/serial numbers for subsequent tracing and identification. At the site, a device accountability system will be maintained during the study and afterwards, documenting device shipment and receipt, storage at the site, use, and return as applicable. Detailed information about the investigational solution can be found in the Investigator's Brochure. See Table 2 for an overview of the manufacturing process and responsibility.

Table 3 Manufacturing of ear-EEG solution

Step	Process description	Responsible
1	Impression of the subjects' ears and measuring of the length of the subject's neck size	Odense University Hospital
1	Production of Recorder and individualized Headsets	T&W Engineering A/S

Study procedures related to ear EEG:

(Physical visit 1A): Ear measurement for individual molding of ear electroencephalography (EEG) research solution:

- Ear impression for individualization of the Headset. Ear measurement is performed by a trained person (medical doctor or study nurse) on site. From the impression, personal earbuds to the Headsets are produced.

Ear EEG setup (physical visit 1B):

- Instructions and handing out ear-EEG solution to patients. Once the Headsets are ready a visual inspection is performed to assess the quality of the earbud fit. This is done using a short recording and manual inspection of the recorded data in term of 50 Hz line noise contamination. The presence of large amounts of 50 Hz noise indicates that the electrodes has insufficient contact to the skin. An EEG channel is accepted, meaning that the underlying electrodes are considered to have a good connection to the skin, when the neural component, being dominated by frequencies well below 50 Hz, is clearly visible in the data trace. If not at least 2 channels in each ear have good connections after repeated cleaning of the skin, the study participant is withdrawn. Additionally, the participant's capability of mounting the earpieces autonomously and uploading data to the external device will be assessed. Furthermore, a training session of completing sleep diary, pain questions and ease-of-use and comfort questionnaire will be completed.

Getting accustomed to repeated ear EEG use (Between visit 1B and visit 2 – home)

- Start 5-day adaption period for sleeping with ear EEG (2 days with; 1 day without; 2 days with). The participant will be sent home with the equipment and asked to sleep with it on the following 2 nights, followed by one night without the device followed by another 2 nights sleeping with the device. This phase is to allow the participant to get accustomed to wearing the device during several nights. The participants are also asked to upload the recorded data each morning to the cloud and recharge the Recorder.

Pre-intervention Ear EEG assessment (Between visit 1B and visit 2 – home)

- After 5-day adaptation period – First week of EEG sleep assessment (5 out of next 7 days). The participant will be asked to sleep with the ear-EEG device for 5 nights in the following week. Participants are encouraged to maintain normal sleeping habits. The participant will upload recordings to provided PC every day. In case of low compliance with EEG recordings or data upload the investigators will contact the participant, clarify and provide necessary support.

During-intervention Ear EEG assessment (Week 4 – home)

- The participant will be asked to sleep with the ear-EEG device for 5 nights during this week. Participants are encouraged to maintain normal sleeping habits. The participant will upload recordings to provided PC every day. In case of low compliance with EEG recordings or data upload the investigators will contact the participant, clarify and provide necessary support.

Return ear EEG solution (Week 6 – physical visit 3):

- Return ear EEG solution. The participant return to the study site for an end of study visit to return the ear-EEG solution.
- Registration of adverse device events, debriefing and completion of the Summative. The PI will explore and register any adverse device events, and ease-of-use and comfort using Ease-of-use and Comfort questionnaire and System Usability Scale.

8.0 Safety evaluation

8.1 Specification and justification of safety parameters

As described in section 2.4 Melatonin is considered safe to use and the risk of serious adverse drug reactions is considered to be low. Liver function and kidney function is assessed before inclusion measuring Serum levels of ALAT, Creatinine and GFR. Urine-hCG is measured with a sensitivity of minimum 25 mIU/ml before inclusion and after 3 and 6 weeks in all fertile women. At week 3, 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.
- Suspected unexpected serious adverse reactions (SUSAR): an adverse reaction that is both unexpected and serious.

AE, AR, SAE, and SAR are registered after 3, 6 and 8 weeks directly in REDCap/eCRF. See more specifically 8.5. The SmPC for Melatonin (see section 2.4) 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 Monitoring of patients in case of adverse events/adverse reactions

Patients are offered follow up at the Pain Center at Odense University Hospital by the primary investigator until adverse events/adverse reactions have ceased or are stable.

8.5 Reporting of serious adverse events and unexpected serious adverse events

If an AE is considered serious, based on the criteria above, it will qualify as an SAE. The investigator will report all SAE's to sponsor immediately but no later than 24 hours after the event. All SAE's are registered in REDCap, so the Sponsor automatically get a notification when a SAE is reported in REDCap. In the REDCap the investigator will also report suspected causality**.**

All SAE's judged by the investigator and/or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as a SAR. 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, it will be considered a SUSAR. In this case, sponsor will unblind the subject and immediately contact the GCP unit for reporting the SUSAR in EudraVigilance.We have a collaboration with the GCP Unit at Odense University Hospital, and they will assist us with the reporting in the EudraVigilance system.

All relevant information about a SUSAR, which is fatal or life-threatening, will be reported in EudraVigilance as soon as possible, and no later than 7 days after the sponsor is made aware. No later than 8 days after the first report, relevant information about the sponsors and investigators follow-up to the report must be entered in EudraVigilance. Any other SUSAR will be reported in EudraVigilance no later than 15 days from the time the sponsor is made aware. All reports must be accompanied by comments on possible consequences for the trial.

Once a year throughout the duration of the clinical trial, the sponsor will provide a list of any SARs and a safety report to the authorities via CTIS.

No more than 15 days after completion of a trial, the sponsor will report in CTIS that the trial has been completed. As soon as possible and no later than one year after the trial has ended, the trial results and a safety report will be reported in CTIS.

In case of a SUSAR unblinding will happen in accordance with the unblinding procedure mentioned at section 4.5.

9.0 Statistics

9.1 Statistical methods

Difference in change from baseline to 6 weeks in the primary outcome (mean NRS pain in past 7 days, continuous) between the intervention and the placebo-control group will be estimated using a mixed linear model approach with time (baseline, 1, 2, 3, 4, 5 and 6 weeks), treatment arm (Melatonin or placebo) and the interaction between time and treatment arm, as fixed effects and intercept and slope as patient-specific random effects (NRS baseline value will be considered a covariate in the model). Difference in change in secondary outcomes from baseline to 6 between the intervention and the placebo-control group will also be estimated using a mixed linear model approach with the respective secondary outcome, time (baseline, 3, and 6 weeks), treatment arm (Melatonin or placebo), the interaction between time and treatment arm as fixed effects and intercept and slope as patient-specific random effects(the respective secondary outcome value at baseline will be considered a covariate in each of the models). The error variance will be allowed to vary over time and across the two arms, except at baseline. The variance-covariance matrix of the random effects will be allowed to vary across the two arms. Interactions will be parametrized as time dependent treatment effects such that the treatment effect at week 6 corresponds directly with the efficacy parameter of interest. The treatment effect at baseline will be set to 0 to reflect randomization. The treatment effect will be expressed as the gain in reduction observed in the intervention arm, i.e. a positive number expresses a favoring of the intervention. The prespecified efficacy analyses will be based on the intention-to-treat (ITT) principle, which includes all participants that are assessed and randomized at baseline. In the case of missing data during the 6-week trial, repeated measures linear mixed models will take this into account automatically, under the assumption that data is missing at random.

Fitting of the mixed models will be based on the restricted maximum likelihood technique. In case of convergence problems, the model will be simplified by additional restrictions on the variance parameters with respect to equality over time and between the two arms.

Sensitivity analyses with respect to the missing at random assumption will be conducted. These analyses will be based on multiple imputation and follow to approaches. First, we will consider a tipping approaches adding to all generated outcome values a constant value delta, mimicking the expectation that missing outcomes values are in reality higher than those we would expect under MAR. The second approach focus on patients in the intervention arm, who stop participation in the trial, i.e. for whom both the outcome values as well as information on the medication is missing after the finally observed outcome. In these patients there is a risk that these patients have stopped the treatment and hence that they start to become comparable to the placebo arm. To address this, in these patients the further increments are generated using the distribution of the increments observed in the placebo arm

in patients with similar values until drop out. Details of these analyses will be fixed in the statistical analysis plan.

With respect to potential non-compliance, also a per-protocol analysis will be performed, with a per protocol population defined as patients with an adherence to the treatment of at least 80%.

At the end of the intervention phase, empty medicine-cans will be returned and any non-ingested medicine will be counted by a trained employer at the Pain Center OUH. Participants will be asked if they lost any of the tablets. Both number of returned tablets and number of lost tablets will be recorded
It is required for the participants to have an adherence of the active medication and placebo of at least 80 % during the study period to be defined as 'compliant'. The study medication and placebo will be counted at the study end visit.

In two separate responder analysis, a responder is defined as a patient who report more than 30% and 50% decrease in pain after 6 weeks, respectively. Treatment differences between treatment arms will be expressed by adjusted odds ratios. These will be based on a logistic regression model including the baseline pain intensity value as covariate.

A detailed statistical analysis plan (SAP) will be made publicly available before the statistical analysis is initiated. The SAP will include a detailed plan of the analysis of all secondary outcomes.

9.2 Trial interpretation

Please refer to table 4 for a detailed overview of the trial interpretation for all possible effect estimates and 95% CI scenarios. A difference of 1 point in the primary outcome is considered clinically relevant.

Table 4 Trial interpretation for different estimate and 95% CI scenarios.

Scenario	Estimate	Lower bound CI	Upper Bound CI	
1.	>=1	>=1		We have demonstrated an intervention effect of clinically relevant magnitude
2.	>=1	>=0, <=1		We have demonstrated an intervention effect and obtained a positive intervention effect estimate of clinically relevant magnitude.
3.	>=1	<=0		We obtained a positive intervention effect estimate of clinically relevant magnitude, but we could not demonstrate an intervention effect

4.	>=0,<=1	>=0	>=1	We have demonstrated an intervention effect and obtained a positive intervention effect estimate.
5.	>=0, <=1	>=0	<=1	We have demonstrated an intervention effect but also the absence of an intervention effect of clinically relevant magnitude.
6.	>=0, <=1	<=0	>=1	We obtained a positive intervention effect estimate, but we could not demonstrate an intervention effect
7	>=0,<=1	<=0	<=1	We obtained a positive effect estimate but also demonstrated the absence of an intervention effect of clinically relevant magnitude.
8.	<=0		>=1	We obtained a negative intervention effect estimate, but we could not exclude that the intervention effect is of clinically relevant magnitude.
9.	<=0		>=0, <=1	We obtained a negative intervention effect estimate and demonstrated the absence of an intervention effect of clinically relevant magnitude.
10.	<=0		<=0	We have demonstrated the absence of a positive intervention effect

10. Direct access to source data/source documents

According to the Danish executive order on GCP, informed consent from patients will also include consent to monitoring, auditing and/or inspection. The investigators are authorized to direct access to 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

The GCP unit at OUH will be responsible for monitoring the study in accordance with the ICH GCP guidelines. Data processing regarding the trial will be reported to the list of on-going research projects via the Executive Secretariat at OUH. Confirmation that standard procedures for quality control and quality assurance will be complied with, cf. ICH GCP guidelines.

12. Ethics

12.1 Ethical considerations

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

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

There are some risk of having side effects from the study medication. The risk of serious adverse reactions from treatment with Melatonin is low. Side effects expected most likely to occur are: Headache and somnolence (i.e. 'common' side effects according to SmPC).

Potential benefits for patients are that they may experience reduced pain-intensity (and improved sleep for those patients with insomnia symptoms). The results from the study will potentially be of benefit for other patients with chronic back pain.

12.2 Recruitment, information and collection of informed consent

Participants for the trial will be recruited through advertisements and social media campaigns. Written information will be send via e-boks to interested patients and be contacted by telephone a few days after receiving the written information. During the telephone call additional oral information will be given, patients will be able to ask questions and patients will respond to initial screening questions for eligibility. It is emphasized that participation is voluntary, and that consent can be withdrawn at any time.

Participants interested in participating in the trial and fulfilling the initial eligibility criteria will be invited to a screening interview and further eligibility examination at the Pain Center at Odense University Hospital (visit 1A). This visit will be at least 24 hours after the screening and study information over the phone. Participants are welcome to bring a lay representative/companion at visit 1A. Before informed consent is collected further oral information about the trial is repeated at visit 1A. It is secured that the information can be given in privacy.

For all patients, oral information will be given by telephone by a study nurse/coordinator/medical student. But a doctor will make the last evaluation of the inclusion/exclusion criteria, and it will also be a doctor who give a detailed information about the study and that collects the informed consent.

13. Handling and filing of data and biological material

13.1 Handling of data

The handling of data will comply with Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (GDPR) and with the Danish Data Protection Act.
Data obtained from the participant's medical file will be data about concomitant medication from the shared medication record and laboratory data (blood tests). No data will be obtained from the participants file, before informed consent is given.
Ear-EEG data will be uploaded directly from participants and stored on secured servers at Aarhus University. Data exchange with collaborators will happen through a secure data sharing service. EEG data will be saved pseudo-anonymized in a data system at Aarhus University to which relevant personnel at the site will have access. Data will be uploaded and transferred to the designated data system directly by the participant on daily basis.
Questionnaire data are collected online using RedCap and entered by the patients.

All other data are entered into the eCRF in RedCap by the primary investigator, the sub investigator or the study nurse.

5 year after termination of the study, the data will be anonymized.

13.2 Handling of biological material

At baseline, blood will be collected for the assessment of liver and kidney function. The blood samples will be analysed at the Department of Clinical Biochemistry at Odense University Hospital, and will be destroyed after analysis. No blood samples will be stored or sent abroad. The samples are processed in compliance with GDPR and the Danish Data protection Act.

14. Financing and insurances

14.1 Insurance

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

14.2 Financing

The study is funded by a grant from Sygesikringen 'danmark' (Health Insurance Denmark):

Salary:

Salary for Prof. Preben Kidmose (responsible for ear EEG)	35,500 DKK
Salary PhD-student Kübra Kilic	1,469,000 DKK
Salary Postdoc (analysis of ear EEG)	138,500 DKK
Salary PI/Sponsor (MD Karin Due Bruun)	190,226 DKK

Salary Project MD	369,000 DKK
Salary Statistician	29,000 DKK
Total salary	2,231,226 DKK
Operating expenses:	
Transport compensation for patients	41,280 DKK
Trial medication	209,950 DKK
GCP monitoring	35,000 DKK
blood tests, pregnancy tests etc.	108,000 DKK
Ear EEG	240,000 DKK
Conference PhD-student	10,000 DKK
Total operating expences	644,230 DKK
Total budget	2,875,456 DKK

The funder (Sygesikringen 'danmark') have no role in the design, conduct or dissemination of the trial.

14.3 Compensation for patients

Patients that reside more than 25 kilometers away from the place of the trial, will receive compensation for expenses for transportation. The compensation fee is 2.19 DKK 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).
The primary report of 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 on the primary report will be PhD-student Kubra Kilic.
Last author on the primary report will be Prof. Jonas Bloch Thorlund.
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.

17. References

1. Diseases GBD, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. Oct 17 2020;396(10258):1204-1222. doi:10.1016/S0140-6736(20)30925-9
2. Collaborators GBDLBP. Global, regional, and national burden of low back pain, 1990-2020, its attributable risk factors, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol*. Jun 2023;5(6):e316-e329. doi:10.1016/S2665-9913(23)00098-X
3. Saragiotto BT, Machado GC, Ferreira ML, Pinheiro MB, Abdel Shaheed C, Maher CG. Paracetamol for low back pain. *Cochrane Database Syst Rev*. Jun 7 2016;(6):CD012230. doi:10.1002/14651858.CD012230
4. Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev*. Feb 10 2016;2:CD012087. doi:10.1002/14651858.CD012087
5. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. *BMJ*. Jan 5 2015;350:g6380. doi:10.1136/bmj.g6380
6. Tang NK, Wright KJ, Salkovskis PM. Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. *J Sleep Res*. Mar 2007;16(1):85-95. doi:10.1111/j.1365-2869.2007.00571.x
7. Bahouq H, Allali F, Rkain H, Hmamouchi I, Hajjaj-Hassouni N. Prevalence and severity of insomnia in chronic low back pain patients. *Rheumatol Int*. May 2013;33(5):1277-81. doi:10.1007/s00296-012-2550-x
8. Bigatti SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. *Arthritis Rheum*. Jul 15 2008;59(7):961-7. doi:10.1002/art.23828
9. Edwards RR, Almeida DM, Klick B, Haythornthwaite JA, Smith MT. Duration of sleep contributes to next-day pain report in the general population. *Pain*. Jul 2008;137(1):202-207. doi:10.1016/j.pain.2008.01.025
10. Xie Z, Chen F, Li WA, et al. A review of sleep disorders and melatonin. *Neurol Res*. Jun 2017;39(6):559-565. doi:10.1080/01616412.2017.1315864
11. Besag FMC, Vasey MJ, Lao KSJ, Wong ICK. Adverse Events Associated with Melatonin for the Treatment of Primary or Secondary Sleep Disorders: A Systematic Review. *CNS Drugs*. Dec 2019;33(12):1167-1186. doi:10.1007/s40263-019-00680-w
12. Xu H, Zhang C, Qian Y, et al. Efficacy of melatonin for sleep disturbance in middle-aged primary insomnia: a double-blind, randomised clinical trial. *Sleep Med*. Dec 2020;76:113-119. doi:10.1016/j.sleep.2020.10.018
13. Oh SN, Myung SK, Jho HJ. Analgesic Efficacy of Melatonin: A Meta-Analysis of Randomized, Double-Blind, Placebo-Controlled Trials. *J Clin Med*. May 21 2020;9(5)doi:10.3390/jcm9051553
14. de Zanette SA, Vercelino R, Laste G, et al. Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: a phase II, randomized, double-dummy, controlled trial. *BMC Pharmacol Toxicol*. Jul 23 2014;15:40. doi:10.1186/2050-6511-15-40
15. Danilov A, Kurganova J. Melatonin in Chronic Pain Syndromes. *Pain Ther*. Jun 2016;5(1):1-17. doi:10.1007/s40122-016-0049-y
16. Andersson E, Kander T, Werner MU, Cho JH, Kosek E, Bjurstrom MF. Analgesic efficacy of sleep-promoting pharmacotherapy in patients with chronic pain: a systematic review and meta-analysis. *Pain Rep*. Jan 2023;8(1):e1061. doi:10.1097/PR9.0000000000001061

17. Hussain SA, Al K, II, Jasim NA, Gorial FI. Adjuvant use of melatonin for treatment of fibromyalgia. *J Pineal Res*. Apr 2011;50(3):267-71. doi:10.1111/j.1600-079X.2010.00836.x
18. Castano MY, Garrido M, Rodriguez AB, Gomez MA. Melatonin Improves Mood Status and Quality of Life and Decreases Cortisol Levels in Fibromyalgia. *Biol Res Nurs*. Jan 2019;21(1):22-29. doi:10.1177/1099800418811634
19. Medicin.dk. Melatonin (Lægemiddelgruppe). www.promedicin.dk
20. Andersen LPH, Gögenur I, Rosenberg J, Reiter RJ. The Safety of Melatonin in Humans. *Clin Drug Investig*. 2016;36:169-175.
21. Schrire ZM, Phillips CL, Chapman JL, et al. Safety of higher doses of melatonin in adults: A systematic review and meta-analysis. *J Pineal Res*. 2022;72:e12782.
22. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. Jan 2005;113(1-2):9-19. doi:10.1016/j.pain.2004.09.012
23. Roland M, Fairbank J. The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. *Spine (Phila Pa 1976)*. Dec 15 2000;25(24):3115-24. doi:10.1097/00007632-200012150-00006
24. Burbridge C, Randall JA, Abraham L, Bush EN. Measuring the impact of chronic low back pain on everyday functioning: content validity of the Roland Morris disability questionnaire. *J Patient Rep Outcomes*. Aug 28 2020;4(1):70. doi:10.1186/s41687-020-00234-5
25. Lauridsen HH, Hartvigsen J, Manniche C, Korsholm L, Grunnet-Nilsson N. Responsiveness and minimal clinically important difference for pain and disability instruments in low back pain patients. *BMC Musculoskelet Disord*. Oct 25 2006;7:82. doi:10.1186/1471-2474-7-82
26. Albert HB, Jensen AM, Dahl D, Rasmussen MN. [Criteria validation of the Roland Morris questionnaire. A Danish translation of the international scale for the assessment of functional level in patients with low back pain and sciatica]. *Ugeskr Laeger*. Apr 28 2003;165(18):1875-80. Kriterievalidering af Roland Morris-sporgeskemaet. Et oversat internationalt skema til vurdering af aendringer i funktionsniveau hos patienter med laendesmerter og iskias.
27. Kamper SJ, Ostelo RW, Knol DL, Maher CG, de Vet HC, Hancock MJ. Global Perceived Effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. *J Clin Epidemiol*. Jul 2010;63(7):760-766 e1. doi:10.1016/j.jclinepi.2009.09.009
28. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol*. Nov 2010;63(11):1179-94. doi:10.1016/j.jclinepi.2010.04.011
29. Dieperink KB, Elnegaard CM, Winther B, et al. Preliminary validation of the insomnia severity index in Danish outpatients with a medical condition. *J Patient Rep Outcomes*. Mar 2 2020;4(1):18. doi:10.1186/s41687-020-0182-6
30. Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. May 1 2011;34(5):601-8. doi:10.1093/sleep/34.5.601
31. Vaegter HB, Thinggaard P, Madsen CH, Hasenbring M, Thorlund JB. Power of Words: Influence of Preexercise Information on Hypoalgesia after Exercise-Randomized Controlled Trial. *Med Sci Sports Exerc*. Nov 2020;52(11):2373-2379. doi:10.1249/MSS.0000000000002396

32. Graven-Nielsen T, Vaegter HB, Finocchietti S, Handberg G, Arendt-Nielsen L. Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: a reliability study. *Pain*. Nov 2015;156(11):2193-2202. doi:10.1097/j.pain.0000000000000294
33. van der Gaag WH, Roelofs PD, Enthoven WT, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for acute low back pain. *Cochrane Database Syst Rev*. Apr 16 2020;4(4):CD013581. doi:10.1002/14651858.CD013581
34. Authority) SDH. *Danskernes Sundhed - Den Nationale Sundhedsprofil 2021*. 2022.
35. Mairey I, Rosenkilde S, Klitgaard MB, Thygesen LC. *Sygdomsbyrden i Danmark - sygdomme*. 2022.
36. Sandal LF, Thorlund JB, Moore AJ, Ulrich RS, Dieppe PA, Roos EM. Room for improvement: a randomised controlled trial with nested qualitative interviews on space, place and treatment delivery. *Br J Sports Med*. Mar 2019;53(6):359-367. doi:10.1136/bjsports-2016-097448
37. Jensen K, Andersen HO, Olesen J, Lindblom U. Pressure-pain threshold in human temporal region. Evaluation of a new pressure algometer. *Pain*. Jun 1986;25(3):313-323. doi:10.1016/0304-3959(86)90235-6
38. Mikkelsen KB, Tabar YR, Kappel SL, et al. Accurate whole-night sleep monitoring with dry-contact ear-EEG. *Sci Rep*. Nov 14 2019;9(1):16824. doi:10.1038/s41598-019-53115-3
39. Kjaer TW, Rank ML, Hemmsen MC, Kidmose P, Mikkelsen K. Repeated automatic sleep scoring based on ear-EEG is a valuable alternative to manually scored polysomnography. *PLOS Digit Health*. Oct 2022;1(10):e0000134. doi:10.1371/journal.pdig.0000134
40. Berry RB, Brooks R, Gamaldo C, et al. AASM Scoring Manual Updates for 2017 (Version 2.4). *J Clin Sleep Med*. May 15 2017;13(5):665-666. doi:10.5664/jcsm.6576