NSAIDS IN SCIATICA (NIS)

AN INVESTIGATOR INITIATED RANDOMISED PLACEBO CONTROLLED TRIAL OF NAPROXEN

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SIGNATURE PAGE

Title	NSAIDs in sciatica (NIS), an investigator initiated randomised placebo controlled trial of Naproxen.
Protocol ID no:	SO-2017-1
EudraCT no:	2014-003623-21

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

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PROTOCOL SYNOPSIS

Title: NSAIDs in sciatica (NIS), an investigator initiated randomised placebo controlled trial of Naproxen.

Sponsor:	Sykehuset Østfold HF
Phase and study type	Phase IV randomized placebo-controlled clinical trial
Investigational Medical Product	Naproxen
Centers:	Sykehuset Østfold HF, Moss Sykehuset Telemark, Porsgrunn Stavanger Universitetssjukehus, Stavanger Oslo universitetssykehus, Ullevål
Study Period:	Estimated date of first patient enrolled: 15 september 2017 Anticipated recruitment period: 7 years Estimated date of last patient completed: 15 september 2024
Treatment Duration:	10 days
Primary objective	To demonstrate that treatment with Naproxen 500 mg twice daily is superior to placebo for the improvement of leg pain intensity in patients with sciatica.
Secondary objectives	To demonstrate that in patients with sciatica treatment with Naproxen 500 mg twice daily is superior to placebo with respect to – improvement of back pain intensity – improvement in disability – the use of Paracetamol as rescue medication – global perceived improvement – improvement in sciatica symptoms – 30% and 50% leg pain improvement – the concomitant use of opioid analgesics – improved ability to work and study
Study Design:	Multicenter, randomised, placebo controlled, double blind, parallel group, superiority trial.

Main Inclusion Criteria:	– Age ≥ 18 years – Radiating pain below the knee with a severity score of ≥4 on a 0-10 (NRS) in the previous 24 hours – Signs of nerve root/spinal nerve involvement as indicated by at least one of the following features; myotomal weakness, dermatomal sensory disturbances (e.g. sensory loss, self-reported tingling/numbness), diminished reflexes, radiating pain exacerbation by SLR
Main Exclusion Criteria	– Not able to read or speak Norwegian. – Unlikely to adhere to treatment and/ or complete follow-up (e.g ongoing serious psychiatric disease, drug abuse, plans to move) – Sciatica of known cause other than disc herniation or degenerative stenosis. – Neurogenic claudication, i.e. pain in the legs on walking or standing that resolves with sitting down or lumbar flexion. – Symptoms indicating immediate surgery: cauda equina syndrome or a progressive large paresis. – Women who attempt to conceive, are pregnant or breastfeeding. – Previous episodes of asthma, urticaria or allergic-type reactions after taking aspirin or other NSAIDs. – Active or history of peptic ulceration, gastrointestinal bleeding, or perforation. – Use of drugs known to increase upper gastrointestinal adverse events in combination with Naproxen: anticoagulants, aspirin (acetyl salicylic acid), serotonin reuptake inhibitors and systemic corticosteroids. – Hepatic enzyme (ASAT/ALAT) values above 1,5 x upper limit of normal (ULN) – Renal function tests (creatinin/eGFR) outside normal range – Congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease. – Known hypersensitivity to Naproxen or any of the excipients (lactose, maize starch, povidone, sodium starch glycolate, talcum, magnesium stearate, polysorbate 80) – Ongoing treatment with diuretics, ACE-inhibitors, lithium – Scheduled for spinal surgery prior to the final study visit – Reservation against intake of gelatine (the capsules contains gelatine, which among other things is produced by ingredients from pigs)
Sample Size:	150 patients
Efficacy Assessments:	Patient reported outcomes daily during the 10 days treatment period.
Safety Assessments:	Record of adverse events and serious adverse events.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AE	Adverse Event
COX	Cyclooxygenase
CT	Computed tomography
DAE	Discontinuation due to Adverse Event
DDD	Defined Daily Dose
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GI	Gastrointestinal
GPC	Global perceived change
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product (includes active comparator and placebo)
MRI	Magnetic resonance imaging
NNT	Number Needed to Treat
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over-the-counter
PRO	Patient Reported Outcome
RCT	Randomized Controlled Trial
REK	The Norwegian Regional Ethics Committee South East
RMDQ-S	Roland Morris Disability Questionnaire modified for use in sciatica
SAE	Serious Adverse Event
SBI	Sciatica Bothersomeness Index
SPC	Summary of Product Characteristics
SLR	Straight leg raising

ULN	Upper limit of normal

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 The term sciatica

Sciatica is an established term for pain along the course of the sciatic nerve, radiating from the lower back or buttock into the leg [1]. Sciatica is also known by terms such as low back-related leg pain, lumbosacral radicular syndrome or radiculopathy.

1.1.2 Causes of sciatica

In principle, sciatica may be caused by any structure affecting the sciatic nerve or nerve roots from L4 to S3. However, lumbar intervertebral disc herniations are considered the by far most common cause.

A disc herniation is a focal deformity of the annulus fibrosis or extrusion of disc material into the spinal canal or neural foramen that may cause stretching and compression of the nerve root and dorsal root ganglion. Herniated discs may cause inflammation of the nearby nerve roots and dorsal root ganglia [2, 3] causing pain, sensory disturbances and muscular weakness. In more than 90% of cases, the L5 and S1 nerve roots are affected, giving rise to pain that radiates below the knee. Herniations affecting the L3 and the L4 roots may cause pain in the thigh or groin. A rare but potentially devastating complication is cauda equina syndrome, involving impaired bladder, bowel, and genital dysfunction. Clinical signs of nerve dysfunction, i.e. abnormal straight leg raising test and (SLR) reduced dermatomal sensibility, muscular strength, or tendon reflexes support the diagnosis of sciatica.

Age-related degenerative changes including facet joint hypertrophy, thickening of the ligamentum flavum and spondylolisthesis, (spinal stenosis), may also cause sciatica. Most patients with symptomatic spinal stenosis report neurogenic claudication, but stenosis of the lateral recess or the nerve root canal may give rise to symptoms resembling those seen in disc herniation [4]. Neurological signs are generally absent.

Occasionally, it may difficult to distinguish between radicular and referred pain. There is some experimental evidence for noxious stimulation of non-neural lumbar structures such as ligaments [5], facet joints [6], or intervertebral discs [7] to cause pain in the leg. In contrast to radicular pain referred pain is generally described as deep and diffuse and neurological signs are absent.

Very rarely, spinal tumours, cysts, haemorrhage, abscesses or fractures may cause sciatica.

1.1.3 Epidemiology

Sciatica is a common condition with a point prevalence of 2–5%, affecting especially the working-age population [8, 9]. In a Dutch general population study of neuropathic pain the reported incidence of sciatica was about 2/1000 [10]. In Sweden [11] 5% of the general working population sought health care for a new episode of low back pain during a 3-year period, 25% of these people reported radiating pain below the knee. In Norway, a diagnosis of low back pain accounts for about 13% of all patients on sick leave and 17% of all compensation days. Of these claimants, 30% have radiating pain [12].

1.1.4 Natural course and prognosis

Sciatica may vary from short-lasting, single episodes to a remitting or permanent course over months or years [13, 14]. Because no population-based prospective study has been performed, the natural course is not fully known. One Dutch study [15] of patients recruited from general practice, reported that 70% of patients had recovered after 3 months. In a study from Norway, Weber [16] included patients within 2 weeks after the onset of radiating pain and found that 40% and 30% still reported pain and reduced working capacity at 3 months and 1 year, respectively. Generally, patients with sciatica have longer absences and lower rates of return to work compared with patients with non-specific low back pain [12, 17, 18]. Our group has previously shown that one-fourth of sick-listed sciatica patients referred to secondary care were still out of work 2 years later [19]. The natural course of sciatica caused by recess or nerve root canal stenosis is not well known but a substantial proportion of patients will remain unchanged or improve without treatment [20, 21].

1.2 TREATMENT OF SCIATICA

Treatment is primarily aimed at pain reduction, either by medication, or surgically by reducing pressure on the nerve root [1]. Drugs commonly used include non-steroidal anti-inflammatory drugs (NSAIDs), analgesics such as paracetamol and opioids, drugs for neuropathic pain, antidepressants and epidural glucocorticoid injections [22]. A systematic review and meta-analysis found however little evidence to support the use of any drug for this condition [23].

1.2.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

Given their analgesic and anti-inflammatory mechanisms of action, NSAIDs have been, and are still being regarded as standard therapy for sciatica [24, 25] [1, 26]. In a survey among american physicians 80% said they would recommend NSAIDs for initial management [27]. In a study from general practice in Italy 90% of the sciatica patients had been prescribed an NSAID. In studies investigating the effect of surgery [28] and manipulation [29], 50-60% of the patients were taking an NSAID at baseline. However, the scientific evidence for this practice is lacking. Very few randomised controlled trials (RCT) of NSAIDs in sciatica have been undertaken, and no study has showed clinically meaningful effects of the NSAID as compared to placebo [30] [31].

The largest study to date investigated the effects of meloxicam 7.5 mg (n=171) and meloxicam 15 mg (n=181) with placebo (n=180) [32]. The difference in overall pain, i.e. back and leg, measured on a 100 mm visual analogue scale (VAS), was 5 points lower in both meloxicam groups than in the placebo group at 1 week. Despite being statistically significant, a between group difference of 5% is not considered clinically meaningful [33]. Another trial, undertaken in Norway between 1988 and 1991, found no differences in leg pain, back pain or disability between piroxicam 20mg (n=120) and placebo (n=94) at two weeks [16]. In two short term studies Bontoux [34] reported a 9% difference in overall pain between placebo (n=61) and etodolac (n=62) and 6% between the same placebo group and diclofenac (n=59) at 27 hours. Herrmann [35], reported significantly less pain (8-10 mm on a 100 mm VAS) 6 hours after intake of lornoxicam (n=57) as compared with placebo.

In patients with sciatica in relation to spinal stenosis no studies have been performed, but NSAIDs are generally recommended [4].

1.2.2 Other drugs

Although the radiating pain is considered of neuropathic origin, drugs approved for the treatment of painful neuropathy, gabapentine and pregabalin, have shown either small or no effect [36] [37, 38]. Neither has the effectiveness of systemic administration of glucocorticoids [39, 40] nor biological agents targeting inflammatory cytokines [41, 42], been established. To our knowledge, the benefit of paracetamol has not been studied in sciatica. In the only study involving opioids, Khomori [43] did not find significant effect on leg pain of sustained release morphine (15 mg/day), antidepressants (nortriptyline 25 mg/day), or a combination of both compared with placebo. Epidural injections of glucocorticoids are considered to have, if any, a small and short lasting effect [44, 45].

1.2.3 Surgery

For patients with disc herniation the current opinion is that if leg pain becomes intolerable or does not diminish after 6-8 weeks surgical treatment (discectomy) may be performed. Discectomy improves the short-term, but not the long-term, prognosis of leg pain, but does not relieve the pain in the lower back [46, 47]. For patients with spinal, foraminal or recess stenosis, laminectomy and partial facetectomy may lead to a more rapid relief of symptoms than non-operative treatment, but symptoms may recur [20, 21].

1.3 CLINICAL EXPERIENCE WITH NAPROXEN

Naproxen is a non-selective NSAID that has been in common use since 1976. Like other NSAIDs it provides analgesic, antipyretic and, in higher doses, anti-inflammatory effects. It is approved for the treatment of inflammatory rheumatic conditions, osteoarthritis, primary dysmenorrhea and musculoskeletal pain, see the Naproxen SPC. According to the Norwegian Prescription Database more than 5 million defined daily dosages (DDD) of Naproxen were prescribed in Norway in 2013. The mechanism of action is to inhibit prostaglandin synthase [cyclooxygenase, (COX)], thereby impairing the transformation of arachidonic acid to prostaglandins. Two isoforms of COX enzymes have been described. COX-1 acts as a housekeeping enzyme regulating normal cellular processes such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function. The expression of COX-2 is usually undetectable in most tissues except in the brain, the kidney, bone

and in the female reproductive system, but is increased during states of inflammation. Naproxen is a non-selective NSAIDs inhibiting both COX-1 and COX-2.

1.3.1 Naproxen and pregnancy

Like other NSAIDs, Naproxen is contraindicated during the third trimester of pregnancy. According to the SPC, Naproxen should not be used during the first two trimesters of pregnancy, unless the potential benefit to the patient outweighs the potential risk to the foetus. In this study pregnancy will be a criterion of exclusion and a pregnancy test will be performed at baseline in in women of childbearing potential. Because naproxen may impair female fertility, women attempting to conceive will not be included in this study.

1.4 RATIONALE FOR THE STUDY AND PURPOSE

1.4.1 Justification for study

Despite lack of evidence, NSAIDs are regarded as standard therapy for sciatica and are in widespread use in clinical practice. NSAIDs involve the risk of serious gastrointestinal, vascular and renal side effects [48-50]. Hence, there is a strong need to clarify their potential beneficial effects in sciatica.

1.4.2 Potential use of study findings

The findings of this study will contribute to guide doctors and patients in the treatment of sciatica.

1.4.3 Description and source of study population

Participants will be recruited among sciatica patients referred to the participating centers. To enhance recruitment primary care clinicians will be invited to refer eligible patients.

1.4.4 Imaging

Lumbar MRI or CT imaging is not a prerequisite for study participation. In patients with images obtained during the current sciatia episode results as reported by the radiologist, will be recorded as background information and categorized as either (i) no changes, (ii) a disc herniation that can explain the symptoms or (iii) other (specified) changes that can explain the symptoms.

1.4.5 How study design addresses hypotheses and meets objectives

A randomised, placebo controlled, double blind trial has excellent internal validity. A parallel-groups design is appropriate since all patients, irrespective of treatment allocation, are expected to improve over time [51, 52]. The study will assess both mean differences in outcomes between those who receive NSAIDs and those who receive placebo as well as responder analyses, e.g. the proportions of patients who report improvement in the two groups. Core outcome domains and measures as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) will be used [33]. Data will be analysed by appropriate methods for repeated measurements, including linear mixed models.

1.4.6 Stakeholder participation

A representative of the Norwegian back pain association, Thor Einar Holmgaard, is a member of the project group.

1.4.7 Rescue medication

A rescue medication protocol including Paracetamol for unacceptable pain wil be provided. Rescue medication can not substitute the study medication. See 5.2.

1.4.8 Rationale for selecting Naproxen as study drug, rather than other NSAIDs

Naproxen was chosen because of evidence that high-dose naproxen, in contrast to other NSAIDs, is not associated with an increased risk of major cardiovascular events [48].

1.4.9 Rationale for Naproxen dose selection

There is evidence for a dose-effect relationship for Naproxen on post operative pain [53] and in patients with hip osteoarthritis the effect on pain increased with the dose in the range from 0.5 g to 1.5 g daily [54]. 1000 mg/day

has been demonstrated to be an effective dose for the treatment of acute or chronic rheumatic conditions, soft tissue injuries and chronic back pain [55-57]. In Norway the approved dose for acute musculosceletal conditions is 750-1000 mg/day in two divided doses. In the current study the dose will be 1000 mg/day in two divided doses. Since the literature suggests a dose dependent effect, a higher dose will be better suited to answering the fundamental question; whether or not Naproxen is helpful for patients with sciatica. Especially, should the study results turn out negative, using a 1000 mg/day dose will prevent objections that the results might have been caused by insufficient doses of Naproxen.

1.5 POTENTIAL RISKS

1.5.1 Potential risks; serious GI events

Naproxen, as other non-selective NSAIDs, is associatied with mucosal injury to the upper gastrointestinal tract, including the development of peptic ulcer disease and its complications, most notably upper gastrointestinal hemorrhage, and perforation [58]. The risk increases moderately for subjects with a history of uncomplicated ulcer, age >65 years, concurrent use of aspirin, corticosteroids or anticoagulants, or a high NSAID dose and is particularly high for those with a combination of two or more these factors or a history of a previously complicated ulcer. Compared with placebo, meta-analyses indicate that Naproxen carries a fourfold increased risk of upper gastrointestinal complications [48, 59]. The risk is dose-dependent; for low daily doses (≤ 500-750 mg) the relative risk has been estimated to about 3, and for high doses (500-750 — 1250 mg) to about 6. These estimates are mainly based on studies on long term users, it is possible that the risk is higher at the beginning of treatment, because susceptible patients may be affected early and stop taking the drug, the 'depletion of susceptbles effect' [60]. A metanalysis of NSAIDs and gastrointestinal events found that except for indometacin non-selective NSAIDs required more than 1 month to induce deleterious effects and that the highest risk occurred at 2-3 months [61].

1.5.2 Potential risks; serious vascular events

According to a recent meta-analysis high-dose naproxen was not associated an increased risk of major cardiovascular events and there was no evidence of an increased risk of stroke [48]. All NSAIDs, including Naproxen doubled the risk of heart failure leading to hospital admission. Another meta-analysis has indicated a small but significant increase in the risk of venous thromboembolism [62].

1.5.3 Potential risks; other adverse events

The tolerability profile of Naproxen is well established [55]. The most frequent adverse events from the double-blind and open-label clinical trials were headache (15%), followed by dyspepsia (14%), and flu syndrome (10%). Other expected AEs of Naproxen are specified in Chapt 8.

1.5.4 Preventive action against potential risks

Patients with a previous ulcer, gastrointestinal bleeding, or perforation and patients who take drugs known to increase upper gastrointestinal adverse events in combination with Naproxen will not be included in this study (see exclusion criteria). Patients with age >65 years will be prescribed a proton pump inhibitor, e.g. omeprazole 20 mg daily, free of charge [63]. Patients with a high risk for serious cardio-vascular events, i.e. patients with congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease will not be included. Other precautions for the use of Naproxen, as specified in the SPC, have been taken into account when specifiying the exclusion and inclusion criteria.

1.6 POTENTIAL BENEFITS

The findings of this study will contribute to guide doctors and patients in the treatment of sciatica. Despite little evidence for being effective NSAIDs are currently regarded as standard therapy for sciatica and are in widespread use in clinical practice. If the results of the present study turn out negative, i.e. the effect is not better than placebo or not considered clinically relevant, future patients can be spared from an ineffective and potentially harmful treatment. Conversely, if Naproxen is shown to be effective, the results of this study will enable the medical community and patients to judge whether the positive effects outweigh the adverse events.

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

2.1 STUDY OBJECTIVE – PRIMARY

- To demonstrate that treatment with Naproxen 500 mg twice daily is superior to placebo for the improvement of leg pain intensity in patients with sciatica.

2.2 STUDY OBJECTIVES – SECONDARY

- To demonstrate that in patients with sciatica treatment with Naproxen 500 mg twice daily is superior to placebo with respect to
    - improvement of back pain intensity
    - improvement in disability
    - the use of Paracetamol as rescue medication
    - global perceived improvement
    - improvement in sciatica symptoms
    - 30% and 50% leg pain improvement
    - the concomitant use of opioid analgesics
    - improved ability to work and study

2.3 PRIMARY ENDPOINT

- The change in leg pain (24 hours average) rated on a 0-10 numeric rating scale (NRS) from baseline to day 10 based on longitudinal analyses of daily observations.

2.4 SECONDARY ENDPOINTS

- The change in back pain (24 hours average) rated on a 0-10 numeric rating scale (NRS) from baseline to day 10 based on longitudinal analyses of daily observations.
- The change in disability assessed by the Roland Morris Disability Questionnaire for sciatica (RMDQ-S) based on longitudinal analyses of observations at baseline, day 5 and day 10.
- The use of rescue medication, i.e. number of Paracetamol tablets taken between baseline and day 10.
- The number of patients who at day 5 and day 10 report their pain to be *completely gone*, *much better* and *better* on a Global Perceived Change (GPC) scale
- The change in sciatica symptoms assessed by the Sciatica Bothersomeness Index (SBI) based on longitudinal analyses of observations at baseline, day 5 and day 10.
- The number of patients who at day 5 and day 10 have a (i) ≥30% and a (ii) ≥50% reduction in leg pain score relative to baseline
- The use of (i) weak opioids and (ii) strong opioids assessed by the number of Defined Daily Doses (DDD) between baseline and day 10
- The number of patients who at day 10 are able to work/study as normal

3 OVERALL STUDY DESIGN

The study is a phase IV, multicenter, randomised, placebo controlled, double blind, superiority, parallel group trial.

Study Period	Estimated date of first patient enrolled: 15 september 2017
	Anticipated recruitment period: 4 years
	Estimated date of last patient completed: 15 september 2021

Treatment Duration: 10 days

4 STUDY POPULATION

4.1 SELECTION OF STUDY POPULATION

4.1.1 Study setting

The study will be performed at outpatient pain/back clinics at public hospitals in Norway, see 1.4.3.

4.1.2 Description and source of study population

See 1.4.3.

4.2 NUMBER OF PATIENTS

150 patients will be included in this trial.

4.3 PRESCREENING

A study coordinator will contact potentially eligible patients at the clinic or by phone, inform about the study and inquire about inclusion and exclusion criteria. A prescreening log including reason for being deemed eligible or not will be established. For patients who are on opioids and do not meet the leg pain intensity requirement of ≥ 4, a new prescreening can be performed 24 hours after last opioid dose.

4.4 INCLUSION CRITERIA

All of the following conditions must apply to the prospective patient at screening prior to receiving study agent (e.g.):

- Age ≥ 18 years
- Radiating pain below the knee with a severity score of ≥4 on a 0-10 (NRS) in the previous 24 hours
- Signs of nerve root/spinal nerve involvement as indicated by at least one of the following features; myotomal weakness, dermatomal sensory disturbances (e.g. sensory loss, self-reported tingling/numbness), diminished reflexes, radiating pain exacerbation by SLR

4.5 EXCLUSION CRITERIA

Patients will be excluded from the study if they meet any of the following criteria:

- Not able to read or speak Norwegian.
- Unlikely to adhere to treatment and/ or complete follow-up (e.g ongoing serious psychiatric disease, drug abuse, plans to move)
- Sciatica of known cause other than disc herniation or degenerative stenosis.
- Neurogenic claudication, i.e. pain in the legs on walking or standing that resolves with sitting down or lumbar flexion.
- Symptoms indicating immediate surgery: cauda equina syndrome or a progressive large paresis.
- Women who attempt to conceive, are pregnant or breastfeeding.
- Previous episodes of asthma, urticaria or allergic-type reactions after taking aspirin or other NSAIDs.
- Active or history of peptic ulceration, gastrointestinal bleeding, or perforation.
- Use of drugs known to increase upper gastrointestinal adverse events in combination with Naproxen: anticoagulants, aspirin (acetyl salicylic acid), serotonin reuptake inhibitors and systemic corticosteroids.
- Hepatic enzyme (ASAT/ALAT) values above 1,5 x upper limit of normal (ULN)
- Renal function tests (creatinin/eGFR) outside normal range
- Congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

- Known hypersensitivity to Naproxen or any of the excipients (lactose, maize starch, povidone, sodium starch glycolate, talcum, magnesium stearate, polysorbate 80)
- Ongoing treatment with diuretics, ACE-inhibitors, lithium
- Scheduled for spinal surgery prior to the final study visit
- Reservation against intake of gelatine (the capsules contains gelatine, which among other things is produced by ingredients from pigs)

4.6 RANDOMISATION AND ALLOCATION

Study medicines will be packaged and labelled according to a pre-generated random number sequence; each sealed box will have a unique participant number. Computer-generated randomisation, stratified by center, will be used. Allocation to Naproxen or placebo will be at a 1:1 ratio.

5 TREATMENT

5.1 INVESTIGATIONAL MEDICINAL PRODUCTS (IMP).

For this study oral Naproxen 500 mg tablets and placebo tablets are defined as IMP.

All IMPs will be encapsulated in Capsugel AAel-capsule. The placebo (vehicle without active drug) will consist of maize starch. Both the Naproxen and the placebo will be encapsulated, packaged and labelled by Kragerø Tablettproduksjon AS, in Kragerø, Norway. The appearance of the containers, labelling and the capsules will be identical for both treatment groups.

5.2 RESCUE MEDICATION

Paracetamol will be provided as rescue for unacceptable pain. Paracetamol can not substitute the study medication.

5.2.1 Paracetamol (acetaminophen)

At baseline the patients will receive a standard package of 100 tablets paracetamol 500 mg free of charge. The dosage will be 1-2 tablets as needed up to a maximum dose of 6 tablets in a 24 hours period. This is a standard dosing approved by The Norwegian Medicines Agency, see the Paracetamol SPC. Paracetamol (acetaminophen) is an established first-line therapy for mild to moderate pain [64]. It has shown analgesic activity in a variety of acute pain syndromes [65, 66] but has not been studied in sciatica. The incidence of adverse effects is low. Overdosing may cause hepatotoxicity but the risk of severe hepatotoxicity from therapeutic doses is considered extremely low [67] [68].

5.3 OTHER PAIN MEDICATION

Patients will be encouraged to avoid pain medication other than study and rescue medication. However, intake of other pain medication will not be classified as a protocol violation. Additional pain medication will be recorded daily by name and classified as (i) weak opioids, (ii) strong opioids or (iii) other and by DDD.

5.4 STORAGE AND ADMINISTRATION

The IMP and the rescue drugs will be stored and administered by collaborating pharmacies and handed out by the responsible pharmacist at the start of intervention. IMP capsules should be swallowed in whole and can be taken with or without food. Patients will be informed to keep the medicine in its original container, in a safe place out of reach of children. The rescue drugs used in this study have a marketing authorization in Norway, thus, the storage and preparation instructions will be according to the the package leaflets.

5.4.1 IMP Dosage and Drug Administration

The IMPs will be administered as fixed doses of 1 tablet (500 mg) twice daily, one tablet in the morning and one tablet in the evening. Thus, the first dose will be 500 mg.

5.4.2 Duration of Therapy

The duration of therapy is 10 days.

5.4.3 Schedule Modifications

There will be no modification of IMP dose or schedule.

5.5 CONCOMITANT MEDICATION

All concomitant medication (incl. OTC drugs) used by the patient will be recorded in the patient's file. Patients will be encouraged not to take any of the following medication during the treatment phase of the study:

- Analgetics or NSAIDs, including over-the-counter (OTC) drugs
- Any new anti-depressant, including SSRIs, tranquillizer, sleep medication, neuroleptics, anti-epiletic drugs not on stable dose before start of the study
- Any of the following: aspirin, systemic corticosteroids, diuretics, ACE-inhibitors, lithium and anticoagulants

All new drugs taken during the study period (10 days) will be recorded in the CRF.

5.6 CONCOMITANT NON-PHARMACOLOGIC TREATMENTS

No non-pharmacologic treatments for pain should be initiated during the trial (e.g., physical therapy, acupuncture).

5.7 SUBJECT COMPLIANCE

Adherence to the medication schedule will be determined by daily self-report in the eCRF, and pill counts at the end of treatment. At day 2 a study nurse/physiotherapist will check the e-CRF for completeness and, if necessary, contact the patient in order to clear up misunderstandings or other issues that may impair compliance. Additionally, at the 5 day follow-up (by telephone) we will inquire about protocol adherence.

5.8 DRUG ACCOUNTABILITY

Drug accountability of the IMPs and the rescue medication will primarily be assessed by pill counts of returned packages. Return, capsule count and destruction of the returned study drug will be administered by the collaborating pharmacies. Generally, pill counts are regarded as being more accurate than self-report or refill history [69]. In case of discrepancy between patients' diaries and pill count, the latter will be used.

5.9 DRUG LABELING

The investigational product will have a label permanently affixed to the outside and will be labeled according with ICH GCP and national regulations, stating that the material is for clinical trial / investigational use only and should be kept out of reach of children. Labelling will be provided by Kragerø apotek including Study name, EudraCT Number, sponsor, center ID, name of PI, patient's initials and birthdate, enrolment code, date dispensed and name of prescribing doctor.

5.10 SUBJECT NUMBERING

Each subject is identified in the study by a unique subject number that is assigned when subject signs the Informed Consent Form. Once assigned the subject number cannot be reused for any other subject.

6 STUDY PROCEDURES

6.1 FLOW CHART

Table 1. Trial flow chart

	Baseline	Start of treatment			Halfway follow-up		End of treatment	Final study visit	Withdrawal
Day	0	1	2	3-4	5 (±1)	6-9	10	12 (±2)	within 7 days after withdrawal
	Visit	Home	Home	Home	Home/ Telephone	Home	Home	Visit	Visit
Informed consent	X								
Inclusion/exclusion	X								
Medical history (including previous use of NSAIDs for sciatica)	X								
Treatment of current sciatica episode	X								
Physical examination*	X								
Vital signs (blood pressure, pulse)	X							X	X
Questionnaires: Leg pain intensity, back pain intensity	X, X†	X	X	X	X	X	X	X	X
Questionnaires: SBI, RMDQ-S	X				X		X	X	X

	Baseline	Start of treatment			Halfway follow-up		End of treatment	Final study visit	Withdrawal
Day	0	1	2	3-4	5 (±1)	6-9	10	12 (±2)	within 7 days after withdrawal
Questionnaire: GPC					X		X	X	X
Questionnaire: Work/study	X						X	X	X
Patient's guess regarding correct treatment								X	X
Self-report of IMD and rescue medication intake		X	X	X	X	X	X		
Protocol compliance, patient discontinuation			X		X			X	
Adverse events, self-report		X	X	X	X	X	X		
Adverse events, investigator					X			X	X
Laboratory tests‡ (safety)	X							X	X
Pregnancy test (women of childbearing potential)	X								
Return of pill boxes								X	X

*SLR, sensory, muscular strength and reflex status of the lower extremities

†On day 0 patients will record back and leg pain both at the clinic and at home in the evening

‡Haemoglobin, hematocrit, leucocytes, thrombocytes, creatinin/eGFR, ASAT, ALAT, ALP

6.2 BY VISIT

6.2.1 Informed consent

Written informed consent will be obtained from all patients, with a copy to the included patients. See appendix B.

6.2.2 Washout

No specific washout procedure will be performed. However, at the day of inclusion patients will be encouraged to avoid analgetics/NSAIDs after bed time. Study medication will start the next morning.

6.2.3 Baseline

- The physiotherapist or physician decides on the inclusion/exclusion criteria and provides study ID.
- Medical history including disease history, corresponding treatment details and concomitant medication used within 28 days of treatment start.
- Clinical status including SLR, sensory, muscular strength and reflex status of the lower extremities, blood pressure and pulse. The clinical examination will be performed by a trained physiotherapist or physician.
- The patient receives log in details for Viedoc Me and completes the baseline questionnaires.
- The patient receives prescriptions and written information about study procedures, see appendix B. Women with childbearing potential will be advised to use a contraceptive during the 10 days of study.
- Study drugs are handed out by collaborating pharmacies.

6.2.4 During Treatment

During the treatment period patient reported outcomes will be recorded on a daily basis via the e-CRF. At day 2 a study nurse/physiotherapist will check the e-CRF for completeness, see 5.7. At day 5 (±1), there will be a follow-up, conducted by telephone.

6.2.5 Final Study Visit

At day 12 (± 2) or within 7 days after withdrawal there will be a final study visit at the clinic. Patients will return all pill boxes for pill count. Questionnaires, vital signs, adverse events and laboratory tests will be performed.

6.2.6 Withdrawal Visit

Patients who withdraw or are withdrawn from the study will will be encouraged to complete the final study visit.

6.3 CRITERIA FOR PATIENT DISCONTINUATION

Patients may be discontinued from study treatment and assessments at any time. The reason for discontinuation will be recorded. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation by the patient
- Safety reason as judged by the Principal Investigator
- Major protocol deviation
- Incorrect enrolment ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- A female patient becoming pregnant
- Patient's non-compliance to study treatment and/or procedures

6.4 PROCEDURES FOR DISCONTINUATION

6.4.1 Patient Discontinuation

The patient is not obliged to give his or her reasons for withdrawing prematurely from the trial. However, a reasonable effort will be made to ascertain the reason, while fully respecting the patient's rights. If he or she is unwilling or unable to to complete of the final study visit he or she will be invited to report safety and efficacy endpoints either in the eCRF or by phone. Special consideration will be given to collect remaining medication and pill boxes. If the withdrawal is exclusively related to the trial drug therapy, this will be classified as a violation of the protocol and the data collection will be continued as specified in 6.2.4 and 6.2.5. Patient discontinuation will be monitored by checking the eCRF at day 2 and at the telephone follow-up at day 5 (±1).

6.4.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the PI or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients
- Cancellation of drug development

The sponsor and principal investigator will inform all investigators, the The Norwegian Medicines Agency and REK (the Norwegian Regional Ethics Committee South East) of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the The Norwegian Medicines Agency and REK will be informed within 15 days.

6.5 ASSESSMENT OF EFFICACY

Patients will be encouraged to record outcomes at the same time of day during the treatment period.

6.5.1 Leg pain

A NRS of average pain intensity in the previous 24 hours will be used. The 0–10 NRS has been recommended as a core outcome measure in trials of chronic pain [33] and has excellent psychometric properties, usability and compliance. It will be solicited by a presentation of the numbers from 0 to 10, with 0 meaning "No pain" and 10 meaning "Pain as bad as you can imagine." The use of a single pain item is supported by the IMMPACT recommendations for assessing pain in clinical trials [33]. Baseline pain will be determined by the average of the two recordings at day 0 (at the clinic and at home in the evening).

6.5.2 Back pain

24 h average back pain will be assessed by a 0-10 NRS as described above.

6.5.3 Disability

The Roland Morris Disability Questionnaire modified for use in sciatica (RMDQ-S) will be used. The RMDQ [70] is one of the most commonly used measures of back pain related activity limitation [71]. The RMDQ-S [72] is a modification inquiring explicitly about both back and leg pain, including 23 questions that can be answered by yes (=1) or no (=0). The RMDQ-S has measurement properties comparable to the original RMDQ [73] and has been used in previous sciatica studies [74-76]. The MIC of the RMDQ-S is approximately 4 points [73].

6.5.4 Sciatica symptoms

Symptoms will be assessed by The Sciatica Bothersomeness Index (SBI) which is comprised of four sciatica symptoms: 1) leg pain, 2) numbness or tingling in leg, foot, or groin, 3) weakness in leg/foot, and 4) back or leg pain while sitting. Each symptom is rated 0-6 and a total score is obtained by summing up the ratings across the four symptoms. We have previously validated the SBI [77] and it has been used as outcome in other large sciatica studies [75, 78].

6.5.5 Drug intake

The patients will record the number of tablets (IMP and Paracetamol) taken each day. Additionally, "Sykehusapoteket" will count the remaining IMP and Paracetamol tablets returned and record the difference from the number handed out at baseline [79]. The patients will also record the use of other pain medication by medication name and dosage on a daily basis.

6.5.6 Global perceived change (GPC)

Global perceived effect will be measured on a verbal rating scale as response to the question: "You joined this study five (resp. ten) days ago. How is your sciatica/back problem now compared to then? Tick one alternative: Completely gone, much better, better, a little better, no change, a little worse, worse and much worse".

6.5.7 Work/study status

Current work or study status will be assessed by self-report; (i) at present I am able to work or study as usual, (ii) at present I am unable to work or study as usual, (iii) other (specify)

6.6 TOLERABILITY ASSESSMENTS

Tolerability will be monitored by laboratory tests and patient's reports of adverse events. At baseline and at the end of treatment the following tests will be performed:

- Complete blood count (hemoglobin, hematocrit, leucocytes, thrombocytes)
- Creatinin, estimated glomerular filtration rate (eGFR)

- Liver function tests (aspartate transaminase (ASAT), alanine transaminase (ALAT), alkaline phosphatase (ALP)

The monitoring of adverse events is described below, see chapter 7.

6.7 PROTOCOL ADHERENCE ASSESSMENTS

Protocol adherence will be assessed by (i) examining the patients' reports in the e-CRF (at day 2) and (ii) a follow-up conducted by telephone (at day 5 ±1). At day 2 we will examine whether IMP intake, rescue medication intake, questionnaire completion and adverse events were reported. At the day 5 (±1) follow-up the same issues will be examined and any problems will be discussed with the patient. Minor divergence from the protocol will classified as a not important (minor) deviation while one that severly affects the quality of data or impacts subjects' safety will be classified as an important (major) protocol violation.

6.8 END OF TRIAL

The end of this trial will be the last visit of the last subject. The Norwegian Medicines Agency will be notified within 90 days after end of trial.

7 SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

7.1 DEFINITIONS

7.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The term AE is used to include both serious and non-serious AEs.

7.1.2 Non-serious AEs

Since the AE profile of Naproxen is well established, non-serious AEs will be recorded, but not reported to the Norwegian Medicines Agency. The same goes for Paracetamol. The eCRF will include a daily checklist including expected non-serious AEs (see section 7.2) as well as space to specify other unpleasant events.

7.1.3 Serious Adverse Event (SAE)

A SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

7.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as an adverse reaction that is both unexpected (not consistent with the applicable product information as defined in section 7.2) and also meets the definition of a Serious Adverse Reaction (SAE, see section 7.1.3). There may be a causal link to the administered product, known as a Serious Adverse Reaction (SAR). There must be a certain degree of probability that the event is harmful, and an undesirable, reaction to the medicinal product in the study, regardless of the administered dosage.

7.2 EXPECTED ADVERSE EVENTS

Expected AEs according to the Summary of Product Characteristics (SPC) for Naproxen will be recorded in the eCRF. Expected AEs in italics will be included in a tick-off list in the eCRF.

7.2.1 Expected non-serious AEs related to Naproxen

- Dyspepsia
- Nausea
- Diarrhea
- Vomiting
- Abdominal pain
- Skin eruption
- Tinnitus
- Headache
- Tiredness
- Dizziness

7.2.2 Expected non-serious AEs related to Paracetamol

- None

7.3 TIME PERIOD FOR REPORTING AE AND SAE

In this study, participation implies daily recording of patient reported outcomes. Concurrently patients will be asked to report any potential AEs on a daily basis. Additionally, at the follow up at 5 (±1) and at the final study visit we will inquire about AEs. During the course of the study all SAEs will be proactively followed up for each patient; events will be followed up to resolution, unless the event is considered by the investigator to be unlikely to resolve due to the underlying disease. Every effort will be made to obtain a resolution for all SAEs, even if the events continue after discontinuation/study completion.

7.4 RECORDING OF ADVERSE EVENTS

7.4.1 Non-serious AEs

Patients may record non-serious AEs on a tick off list including 10 events expected for Naproxen, see section 7.2.1. Additionally, patients may report other non-serious AEs in their own words. At the follow-up at 5 (±1) at the final study visit the investigator will record whether the event is resolved or still ongoing and whether any action was taken.

7.4.2 Serious AE

The investigator will record the following information in the CRF:

The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).

The duration of the event will be described in terms of event onset date and event ended data.

The intensity of the adverse event will be classified as Mild / Moderate / Severe; according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).

The Causal relationship of the event to the study medication will be assessed as one of the following:

- Unrelated. There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.
- Unlikely. There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.
- Possible. There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.
- Probable. There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.
- Definite. There is a reasonable causal relationship between the investigational product and the AE.

Action taken: The outcome of the adverse event – whether the event is resolved or still ongoing.

7.5 REPORTING PROCEDURE

7.5.1 AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in section 7.1.1 will be recorded in the patient's CRF.

SAEs will be be reported by the investigator to the sponsor, Waleed Ghanima, Forskningsavdelingen, Sykehuset Østfold, Tel 08600; cell phone +47 41303440; E-mail: Waleed.Ghanima@so-hf.no, within 24 hours after the site has gained knowledge of the SAE. Every SAE will be documented by the investigator on the SAE pages in the CRF. The SAE Report Form will be completed, signed and sent to sponsor. The initial report will promptly be followed by detailed, written reports if necessary. The initial and follow-up reports will identify the trial subjects by unique code numbers assigned to the latter.

The sponsor will keep detailed records of all SAEs reported by the investigators and performs an evaluation with respect to seriousness, causality and expectedness.

7.5.2 SUSARs

SUSARs will be reported to the The Norwegian Medicines Agency and REK according to national regulation. The following timelines will be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Norwegian Medicines Agency and REK in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

All other suspected serious unexpected adverse reactions will be reported to the The Norwegian Medicines Agency and to REK as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor. SUSARs will be reported using the CIOMS form.

7.5.3 Annual Safety Report

Once a year throughout the clinical trial, the sponsor will provide the Norwegian Medicines Agency with an annual safety report DSUR.

7.5.4 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

7.6 PROCEDURES IN CASE OF EMERGENCY

The principle investigator will assure that there are procedures and expertise available to cope with emergencies during the study. All patients will at inclusion receive a card with contact information about the sponsor and local investigator, as well as emergency contact information. In the event of an SAE, the Investigator may only break the treatment code if the appropriate future management of the patient necessitates knowledge of the current treatment.

8 DATA MANAGEMENT AND MONITORING

8.1 CASE REPORT FORMS (CRF)

8.1.1 Electronic case report forms (eCRFs)

Patients and designated investigator staff will enter the data required by the protocol into the eCRF. A web-based eCRF software solution, Viedoc™ and ViedocMe™ (Uppsala, Sweden) will be used. ViedocMe™ lets patients report data through their phone, Pc or tablets. Viedoc is approved for use in clinical trials by Oslo University Hospital and is supported by the Norwegian Clinical Research Infrastructures Network (NorCRIN). In order to maximize data quality study participants will receive daily reminders via sms text messages at an agreed time. If any assessments are omitted the eCRF program will send automatic reminders with a copy to the study coordinator. The coordinator will be of help to solve practical problems and encourage the patients to complete the study forms. In case the patient is unable to log into the eCRF or the web site is unavailable, the study coordinator may enter data obtained by a telephone or personal interview. Viedoc will enable identification of patient data recorded by a coordinator. After database lock, electronic copies of the subject data will be archived at the investigational site.

8.1.2 CRF paper back-up

All patients will receive a paper CRF which can be used if the eCRF is unavailable. In such cases, the paper CRF will be source data and a study collaborator will enter the data into the eCRF.

8.2 SOURCE DATA

The following points will be described in the medical records of each patient:

- That the patient is participating in the study, e.g. by including the enrollment number and the study code
- Date when Informed Consent was obtained from the patient
- Results of all assessments confirming a patient's eligibility for the study
- Diseases (past and current; both the disease studied and others, as relevant)
- Results of assessments performed during the study
- Visits to the clinic / telephone contacts during the study, including those for study purposes only
- Serious Adverse Events (if any) including causality assessments
- Date of, and reason for, discontinuation from study treatment
- Date of, and reason for, withdrawal from study
- Date of death and cause of death, if available

Patient reported outcome (PRO) measures will not be recorded in the electronic patient journal system but directly into the eCRF and the eCRF will be source data. If they are recorded on paper and then entered into the eCRF, then the paper CRF is source data. Results of laboratory tests will be entered by a study collaborator and the patient journal will be source data. Results of clinical findings will be entered directly into the eCRF.

8.3 STUDY MONITORING

Department of Clinical Research Support, Oslo University Hospital, will be appointed to monitor this study. The study monitor will visit the center(s) regularly checking the following:

- Reporting of adverse events and all other safety data
- Adherence to protocol
- Maintenance of required regulatory documents
- Study Supply accountability
- Facilities and equipments
- Data completion on the eCRFs including source data verification.

The monitor will review the relevant eCRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required. Monitoring of data completion will be performed within the eCRF solution. When the study monitor has verified the CRFs, the data will be locked for further handling and statistical evaluation. The monitor will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

8.4 CONFIDENTIALITY

The investigator will arrange for the secure retention of the patient identification and the code list. The PI will store a hard copy list including all participants in locked cabinets at Sykehuset Østfold. The PI and one of the co-investigators will have acess to the code list.

8.5 DATABASE MANAGEMENT

During the study eCRF-data will be retained at Viedoc. After locking, the data file will be imported into a designated database at Sykehuset Østfold. All information concerning the study, including the Site File, will be stored for 15 years at Sykehuset Østfold, inaccessible to unauthorized personnel. Data management will be under the guidance of Department of Clinical Research Support, Oslo University Hospital.

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on a mean difference between the Naproxen group and the placebo group of 1.5 (0-10) at ten days with a SD of 2.5 using a two-sample t test. There is no robust evidence for the smallest worthwhile

between group pain relieving effect in sciatica. In previous sciatica studies sample size were calculated based on between group differences of 1.5 and 1.0 [80, 81]. In a recent RCT of pregabaline the sample size was calculated based on a between group difference of 1.5 [36]. In knee osteoarthritis, a condition in which NSAIDs are generally recommended, the treatment effect of NSAIDs is about 1.0 [82-84]. The estimated SD of 2,5 is based on a recent Cochrane review of NSAID studies in sciatica [30].

Assuming 90% power and a two-tailed 5% significance level a sample size of 60 subjects is needed in each treatment arm. Allowing for a combined dropout and non-compliance rate ≤ 20% [85] the total number of subjects will be 150.

9.2 RANDOMIZATION

9.2.1 Allocation- procedure to randomize a patient

Trial participants will be assigned to NSAID or placebo based on a simple (unrestricted), 1:1, randomization approach. Stratifying by center will be performed by block randomization. Viedoc™ will establish a computer-generated allocation sequence list which will be used by Kragerø Tablettproduksjon AS to number the study medicines. The allocation list will be concealed for all other study personell and patients. A copy of the allocation list will be stored by the Department of Clinical Research Support, Oslo University Hospital.

9.2.2 Blinding and emergency unblinding

Patients, investigators, pharmacists and data analyst will be blinded to treatment allocation. Un-blinding of the treatment allocation is permissible only if the safety and well-being of the patient is being compromised. The decision to reveal the treatment allocation during the study may only be done by the Principal Investigator. A copy of the allocation list will be stored by Klinisk forskningsstøtte OUS who will be responsible for unblinding during business hours. Additionally, the Principal Investigator (Anne Julsrud Haugen) can be contacted 24/7 on telephone (+47) 91 19 34 52 for unblinding.

The date and time of un-blinding will be documented in the eCRF and in the patient's hospital records. In the event of an SAE, the Investigator will only break the treatment code if the appropriate future management of the patient necessitates knowledge of the current treatment.

9.2.3 Assessment of patient blinding

At the end of treatment (day 10), or at withdrawal, patients will be asked to guess what treatment they have received. The response categories will include (i) Naproxen, (ii) placebo and (iii) don't know. Descriptive data (2x3 table) will be presented, no statistical analyses will be performed [86].

9.3 POPULATION FOR ANALYSIS

The following populations will be considered for the analyses:

- Intention to treat (ITT) population: All randomized participants, regardless of protocol adherence.
- Safety population: Includes all subjects who have received at least one dose of study medication. Subjects who withdraw from the study will be included in the safety analysis. A list of withdrawn subjects, with the reasons for withdrawal, will be generated.

9.4 PLANNED ANALYSES

Deviation from the original statistical plan will be described and justified in the Clinical Study Report.

9.4.1 Blinded analyses

To minimize the chance of misleading interpretations of the study results, data will be analyzed blinded to the randomization codes [87]. Depending on treatment group, the randomizer will provide each of the participants with a code, A or B, leaving the investigators uncertain if A or B represents Naproxen or placebo. Before unblinding, a summary of data interpretation assuming that treatment A is Naproxen, and assuming treatment B is Naproxen, will be prepared.

9.5 STATISTICAL ANALYSIS

9.5.1 Statistical methodology

The primary analyses will be performed by linear mixed effects models for repeated measures (MMRM) [88]. Mean changes from baseline will be analyzed using a restricted maximum likelihood (REML) based repeated measures approach. Analyses will include the categorical effects of treatment and treatment-by-visit interaction as fixed covariates and intercept as a random variable. Additionally, responder analyses comparing the percentage of patients who have

improved according to predefined cut-offs in the two groups (see 2.2), will be performed using a χ^2 test [89]. The strategy for dealing with missing values will be decided during the blind review of the data at the end of the trial. A statistical analysis plan will be prepared and made accessible at clinicaltrials.gov.

10 STUDY MANAGEMENT

10.1 INVESTIGATOR DELEGATION PROCEDURE

The principal investigator is responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. She will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

10.2 PROTOCOL ADHERENCE

Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the Clinical Study Report .

10.3 STUDY AMENDMENTS

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) will be notified to and approved by the The Norwegian Medicines Agency and the REK according to EU and national regulations.

10.4 AUDIT AND INSPECTIONS

Authorized representatives of a The Norwegian Medicines Agency and REK may visit the centre to perform inspections, including source data verification. Likewise the representatives from the sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice, and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

11 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

11.1 ETHICS APPROVAL

The study protocol, including the patient information and informed consent form to be used, has been approved by the Norwegian Regional Ethics Committee South East (REK) at 29 Jun 2017.

11.2 OTHER REGULATORY APPROVALS

The study has been approved by the Norwegian Medicines Agency at 15 Jun 2017. The study has been registered in the EU ClinicalTrials Register (EudraCT Number: 2014-003623-21).

11.3 INFORMED CONSENT PROCEDURE

The patient information and consent forms are attached in Appendix B. A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder and also scanned to be part of the patient's electronic medical record at the hospital.

11.4 SUBJECT IDENTIFICATION

A paper-based list of all patients (who have received study treatment or undergone any study specific procedure) including a unique code number, patient's initials, date of birth and personal number, full names, addresses, phone-numbers will be established and securely stored at the Dep of Rheumatology, Sykehuset Østfold. In the CRFs the patients will be identified by the corresponding code numbers and initials.

12 TRIAL SPONSORSHIP AND FINANCING

The currents study is investor-initiated. We will apply for grants from Sykehuset Østfold, Helse Sør Øst and other potential sources for research funding.

13 TRIAL INSURANCE

The Principal investigator will have insurance coverage for this study through membership of Legemiddelansvarsforeningen LAF (the Norwegian Drug Liability Association).

14 PUBLICATION POLICY

All personnel who have contributed significantly with the planning and performance of the study will be included in the list of authors. Upon study completion and finalization of the study report the results of this study will be submitted for publication in a peer reviewed journal. Final reports will also be submitted to the The Norwegian Medicines Agency (EMA Study Report) and to REK in accordance with national regulations.

15 REFERENCES

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