A Three Arm Double blind, Randomised, Multicenter Study to investigate the Non-Inferiority of a Soft Gel Capsule of Ibuprofen Lipid Formulation (total daily dose 1200 mg) versus a standard Soft Gel Ibuprofen capsule (total daily dose 1200 mg and 2400 mg) in the Treatment of Patients with Episodic Knee Arthralgia/Flaring Knee Pain.

Published: 09-12-2014
Last updated: 21-04-2024

The principal aims of the study are to assess: 1. The effectiveness of a 5 day treatment course in arresting/ resolving episodic knee arthralgia/ flaring knee pain.2. The relative effectiveness of a low dose (1200 mg/day) of lipid formulated...

Ethical review	Approved WMO
Status	Pending
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON41746

Source
ToetsingOnline

Brief title
FLARE study

Condition

- Joint disorders

Synonym
Knee arthralgia, Knee pain

Research involving
Human

Sponsors and support

Primary sponsor: Infirst HEALTHCARE Ltd
Source(s) of monetary or material Support: opdrachtgever onderzoek

Intervention

Keyword: ibuprofen, knee arthralgia, knee pain, ostheoarthritis

Outcome measures

Primary outcome

Primary endpoint

* Change in pain subscale of the WOMAC after 5 days of treatment.

Secondary outcome

Key secondary endpoint

* Gastrointestinal Symptom Rating Scale (GSRS) questionnaire scores after 5 or

10 days of treatment.

Other Secondary endpoints

* Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain

subscale score after 10 days of treatment.

* Change in WOMAC subscale scores for function and stiffness after 5 days of

treatment and after 10 days of treatment (if the episode has not resolved after

5 days), together with the WOMAC total score.

* Numerical Rating Scales (NRS) for pain, stiffness, function

(patient-nominated activity) and swelling.

* Time to initial resolution of flare, defined as 2 consecutive days with

average daily knee pain intensity of <4/10 (NRS).

* The GSRS subscale scores at baseline and after 5 and 10 days of treatment (if

the episode has not resolved after 5 days).

* End of treatment assessment of knee flare (after 5 and/or 10 days of

treatment).

* PGA of overall knee flare (0-10 NRS) (after 5 or 10 days of treatment).

* OMERACT definition of response (at EOT).

Safety

* Subject reported adverse events (AEs).

Study description

Background summary

Frequent knee pain affects approximately 25% of adults, limits function and mobility, and impairs quality of life. Although knee pain is the most common presenting symptom the aetiology of knee pain in knee osteoarthritis is not well understood episodic flares (acute exacerbations, flare-ups) are recognised as an intermittent, disabling feature of osteoarthritis pain and can be experienced at all stages of the condition, including early in the disease process. The pathological process underlying these episodic flares is unclear although there is evidence for an inflammatory component.
Ibuprofen is the most commonly used and most frequently prescribed nonsteroidal anti-inflammatory agent (NSAID). It is well tolerated and has a well-established safety profile. The incidence of gastrointestinal side effects may be related to the daily dosage and/or the formulation used. Ibuprofen is considered to have a good gastrointestinal tolerability profile when administered at a maximum daily dose of 2400 mg and ranks among the safest of NSAIDs in short term use when assessed by endoscopy. As with many NSAIDs the mechanisms associated with gastric erosion include both topical irritancy

associated with the physiochemical properties (acidity and lipophilicity) of an active ingredient, and also inhibition of prostaglandin synthesis. Reducing the dosage of ibuprofen without impairing efficacy is therefore an important therapeutic goal. Studies have shown ibuprofen at high (2400 mg/day) or low doses (1200 mg/day) to be at least as effective as paracetamol (4000 mg/day) in relieving pain in patients with osteoarthritis of the knee over 4 weeks. Moreover ibuprofen (1200 mg/day) for 6 days was found to be at least as effective as paracetamol (4000 mg/day) in the treatment of pain from osteoarthritis of the knee and ibuprofen was better than paracetamol in patients with moderately severe or severe baseline pain.
The present study investigates the non-inferiority and compares the efficacy and safety of a low dose regimen of a new soft capsule lipid formulation of ibuprofen (maximum daily dose of 1200 mg/day) with a standard dose ibuprofen (low daily dose of 1200 mg/day and high daily dose of 2400 mg/day) routinely prescribed for patients with pain associated with knee osteoarthritis. The proposed lipid formulation fully dissolves ibuprofen within a lipid matrix (lipid excipients hard fat and glycerol monolinoleate), which is anticipated to reduce the acidic effects within the stomach which occur during the dissolution of conventional ibuprofen tablets and capsules, and may reduce gastric irritation associated with ibuprofen exposure.

Study objective

The principal aims of the study are to assess:
1. The effectiveness of a 5 day treatment course in arresting/ resolving episodic knee arthralgia/ flaring knee pain.
2. The relative effectiveness of a low dose (1200 mg/day) of lipid formulated ibuprofen capsule in comparison with a. low dose (1200 mg/day) and a high dose (2400 mg/day) traditionally formulated ibuprofen capsule.
3. Patient reported side effects, in particular GI side effects for all treatment arms.
Primary Objectives
To determine if a 5 day treatment course of 1200 mg/day of ibuprofen in lipid formulation is non inferior to standard ibuprofen capsules (either 1200 mg/day or 2400 mg/day) for the pain subscale of the WOMAC in subjects suffering from episodic knee arthralgia/knee flare pain.

Key secondary objective
To determine if a 5 day treatment course of ibuprofen in lipid formulation (1200 mg/day) is superior to standard soft gel ibuprofen capsules (1200 mg/day and 2400 mg/day) for patient-reported gastrointestinal function-related quality of life using the Gastrointestinal Symptom Rating Scale (GSRS total score). This objective will assess the utility of the GSRS in assessment of gastrointestinal symptoms associated with ibuprofen exposure.

Other secondary objectives
To compare soft gel capsules of ibuprofen lipid formulation (1200 mg/day)

versus standard soft gel ibuprofen capsules (1200 mg/day and 2400 mg/day) in terms of changes in:
* The WOMAC total score and subscale scores for function and stiffness after 5 and 10 days of treatment.
* The WOMAC pain subscale for pain after 10 days of treatment.
* Average daily knee pain intensity (daily 0-10 NRS).
* Function (patient-nominated activity performance) (daily 0-10 NRS).
* Patient assessment of stiffness (daily 0-10 NRS).
* Patient assessment of swelling (daily 0-10 NRS).
* GSRS dimensions of diarrhoea, indigestion, constipation, abdominal pain and reflux syndromes (after 5 and 10 days of treatment).
* Time to first resolution of flare, defined as 2 consecutive days with average daily knee pain intensity of <4/10 (0-10 NRS).
* Patient's global assessment (PGA) of their overall knee flare (0-10 NRS) (after 5 or 10 days of treatment).
* Patient's assessment of outcome at EOT (after 5 and/or 10 days of treatment).
* OMERACT (Outcome Measures in Rheumatology) definition of response (at EOT).
Safety
To evaluate and compare the safety and tolerability of the three treatment arms.

Study design

3-arm, double blind, randomised, multicenter study.

Intervention

Subjects will be randomised to one of three treatment arms.
* Treatment 1: subjects will receive 200 mg soft gel capsule of ibuprofen lipid formulation, and be instructed to take two capsules three times daily (total daily dose: 1200 mg) for 5 days (15 doses).
* Treatment 2: subjects will receive 400 mg soft gel capsule of ibuprofen formulation plus a placebo, capsule and be instructed to take one 400 mg soft gel capsule plus one placebo capsule three times daily (total daily dose: 1200 mg) for 5 days (15 doses).
* Treatment 3: subjects will receive 400 mg soft gel capsule ibuprofen, and be instructed to take two capsules three times daily (total daily dose: 2400 mg) for 5 days (15 doses).

Study burden and risks

Burden: Subjects will need to attend for 2 or 3 study visits depending on whether they require 5 or 10 days of treatment. They will be asked about their medical history and current medications and a physical examination will be completed, including vital signs. Women of childbearing potential will have a urine pregnancy test at baseline and at the end of the study.

Subjects will be asked to complete four questionnaires and record when they take their study medication - this is all done via a patient diary.
Two of the questionnaires are completed 2 or 3 times (depending on whether additional treatment is required), one is completed daily and the fourth is completed at the end of treatment (after 5 days and after 10 days, if required).

Risks associated with participating: there is a risk that subjects may experience side effects associated with the study treatment. As the active ingredient for both treatments is ibuprofen, the side effects are well known although, as with any research study, the study medication may involve unknown risks. This is explained to subjects in the information sheet.

In addition, ibuprofen must be used with caution if subjects are taking certain medications or if the patient is on a low salt diet or is fructose intolerant. This will be reviewed by the subject's GP and also by the study doctor when considering a subject's eligibility for inclusion in the study.

It is possible that if the capsules are given to a pregnant woman they will harm the unborn child. Pregnant women are therefore excluded from the study and women who are at risk of pregnancy shall be asked to have a pregnancy test before taking part.

Benefit: As both the study treatments are effective anti-inflammatory analgesics it is likely that the subjects will receive some benefit from their use in relation to their knee flare.

The Sponsor has a responsibility to monitor all adverse events on the safety database including any adverse event suggestive of a potential bleed. Study medication will be stopped in any patient reporting gastric symptoms of concern (e.g. severe abdominal pain; melaena), at the discretion of the study investigator and after discussion with the IFH designated Medical Safety Physician. Should any such event occur the Ethics Committee would be informed within 2 business days in addition to usual Regulatory reporting requirements. In addition, a monthly study status progress report will be submitted to the Ethics Committee including all events.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1 Male or female subjects between 18 and 70 years of age on the day of signing informed consent.
2 Noticeable pain in the index knee joint lasting >48 h at least 1 time during the previous 12 months either non treated or, requiring non-steroidal anti-inflammatory drugs (NSAIDs).
3 Subjects must rate knee pain as 5 or above based on pain specific NRS.
4 Willingness to abstain from the use of non-study pain medication (apart from paracetamol taken as advised by the Investigator, if required) from the time of onset of knee flare until receipt of study medication.
5 Willingness to abstain from use of NSAIDs (oral and topical other than those given as study treatment), other topical pain therapies (e.g., capsaicin), corticosteroids (systemic and intraarticular), viscosupplementation, and other pharmacological pain treatments during the study.
6 Female subjects of childbearing potential must have a negative urine pregnancy test at screening unless they are surgically sterile or have been post-menopausal for * 1 year (12 consecutive months without menses).
7 Female subjects of childbearing potential must use a medically acceptable means of birth control and agree to continue its use during the study and for at least 30 days after the last dose of study treatment. Medically acceptable forms of birth control include, oral contraceptives, injectable or implantable methods, intrauterine devices, tubal ligation (if performed > 1 year before screening), or double barrier contraception.
8 Subjects must be able to understand and be willing to sign the informed consent prior to

randomisation and agree to the study procedures.

Exclusion criteria

1 History of serious illness or disease (e.g. stroke), progressive neurological signs, septic arthritis, fractures or significant injury or surgery to the knee(s) in the last 3 months.
2 Subjects who have undergone cholecystectomy.
3 BMI < 18 or >39 kg/m2 or a body weight <40 kg.
4 Diagnosis of systemic lupus erythematosus (SLE), mixed connective tissue disorders or autoimmume arthritis (e.g. rheumatoid arthritis, psoriatic arthritis) or receiving disease modifying anti-rheumatic drugs (DMARDs) or biologics.
5 Diagnosis of gout or use of allopurinol, febuxostat, colchicine.
6 Intra-articular corticosteroid to the index knee joint within 3 months prior to baseline visit or to any other joint within 4 weeks prior to screening; hyaluronic acid intra-articular injection to the index knee joint within 6 months prior to baseline visit; systemic corticosteroids (oral, intramuscular or intravenous) within 4 weeks prior to baseline visit.
7 Radiotherapy for chronic articular pain within 3 months prior to baseline visit or planning the initiation of such therapy during the study.
8 Pain medication - medications for treating chronic pain (this refers to all pain medication including but not limited to (including long term regular use of NSAIDs, opiates, anticonvulsants, tricyclic antidepressants, unselective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, etc.) within 4 weeks prior to baseline visit [Note long term regular use is full daily dose as recommended on SmPC or prescribed, daily, for a minimum of 2 consecutive weeks]; or
Pain medications taken on an intermittent basis are permitted as long as a dose has not been taken within 7 days prior to baseline visit and are not taken throughout the duration of the study (this includes NSAIDS and opiates)
9 Subjects taking selective serotonin reuptake inhibitors [SSRIs].
10 Any medication taken to alleviate pain specifically related to the current knee pain and prior to first dose of study medication other than a single dose of 2 x 500mg of paracetamol..
11 Clinically relevant history of hypersensitivity or allergy to study treatment or any other constituent of the drug: History of asthma, acute rhinitis, angioedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid, ibuprofen, or other NSAIDs, including COX-2 inhibitors.
12 Any medical condition other than pain due to OA that could interfere with study evaluations, e.g., anatomical deformities, fibromyalgia, chronic pain syndrome and neuropathy which would interfere with the assessment of pain.
13 Severe heart failure and congestive heart failure; history of clinically significant cardiovascular disease including, but not limited to, myocardial infarction, unstable angina, peripheral arterial disease, and stroke or transient ischemic attack; uncontrolled hypertension.
14 Active or previous history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding) or history of gastrointestinal bleeding or perforation related to previous NSAIDs therapy; history of gastrointestinal bleeding, history of inflammatory bowel disease.

15 Subjects with severe hepatic insufficiency
16 Subjects with renal function GFR <60 mL/min/1.73 m2 based on the MDRD equation.
17 Subjects with rare hereditary problems of fructose intolerance.
18 Any clinically significant condition that in the Investigator*s judgment may affect efficacy or safety assessments or may compromise the subject*s safety during study participation.
19 Participation in any investigational clinical study within 3 months prior to baseline visit.
20 History within the previous 2 years or current evidence of drug or alcohol abuse.
21 Pregnant or lactating women.
22 Any condition or circumstances which in the opinion of the Investigator may make a subject unlikely or unable to complete the study or comply with study procedures and requirements, or may pose a risk to the safety of the subject.
23 Subjects taking anticoagulant therapy

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	02-03-2015
Enrollment:	210
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Flarin 400 mg capsules [Comparator product]
Generic name:	ibuprofen 400 mg (soft gel capsule)
Registration:	Yes - NL outside intended use

Product type:	Medicine
Brand name:	Not applicable
Generic name:	200 mg soft gel capsule Ibuprofen lipid formulation
Product type:	Medicine
Brand name:	Not applicable
Generic name:	placebo

Ethics review

Approved WMO Date:	09-12-2014
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	26-02-2015
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	10-04-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	02-06-2015

Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	12-10-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	16-10-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	18-11-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	20-11-2015
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-004254-33-NL
CCMO	NL51640.072.14