Randomized, 16-Week, Multi-Phase, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fulranumab as Monotherapy in Subjects with Signs and Symptoms of Osteoarthritis of the Hip or Knee

Published: 14-04-2015
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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON42211

Source
ToetsingOnline

Brief title
42160443PAI3003: Fulranumab study in osteoarthritis patients

Condition

- Joint disorders

Synonym
arthritis, osteoarthritis

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen Research & Devlopment

Intervention

Keyword: 42160443PAI3003, Fulranumab, osteoarthrits hip or knee, Phase 3

Outcome measures

Primary outcome

Co-primary Efficacy Endpoints: Changes from baseline to the end of the 16-week

double-blind phase in

the WOMAC pain and physical function subscale scores and PGA score (for US FDA

and Health

Canada only).

Secondary outcome

Secondary Efficacy Endpoints: Change from baseline to the end of the 16-week

double-blind phase in

scores in: PGA score (not for US FDA and Health Canada), NRS for the study

joint, WOMAC Stiffness

subscale, Medical Outcomes Study (MOS) sleep scale, Short-Form-36 Health Survey

(SF-36) subscales,

EuroQol, 5 dimensions, 5 levels (EQ-5D-5L) scales, rescue medication use, as

well as responder rates

based on WOMAC pain and physical function subscales and PGA, separately, and

responder rates for

Outcome Measures in Rheumatology initiative/Osteoarthritis Research Society

(OMERACT-OARSI),

Patient Acceptable Symptom State (PASS), Minimal Clinically Important

Improvement (MCII).

Exploratory Efficacy Endpoints: Changes from baseline to the end of the 16-week

double-blind phase in:

Australian/Canadian Osteoarthritis Hand Index (AUSCAN) scales for subjects with

a pre-study

diagnosis of OA of the hand.

Study description

Background summary

This Phase 3 study will examine the efficacy, safety, and tolerability of 4 injections of fulranumab compared with placebo as monotherapy in subjects with signs and symptoms of OA of the hip or knee that are not adequately controlled by current pain therapy and who have scheduled or who are planning a joint replacement surgery. The pain experienced by this population can affect function, therefore, it is appropriate to evaluate the effect of fulranumab on both pain and physical function. Significant improvement in both areas was previously shown in Phase 2 studies.
This study will provide data to support a product approval.

The hypothesis is that, as monotherapy, at least 1 of the 2 fulranumab doses is statistically significantly
more effective than placebo in changes from baseline in each of the 2 co-primary endpoints: WOMAC
pain and physical function subscales scores after 16 weeks of treatment.

This protocol fulfills global health authority requirements. The differences in the protocol to account for
requirements specific to the US FDA and Health Canada are shown in italics.

Study objective

The primary objective is to demonstrate the efficacy using 2 co-primary endpoints (as measured by the
changes from baseline to the end of Week 16 in Western Ontario and McMaster University
Osteoarthritis Index [WOMAC] pain and physical function subscales), safety, and tolerability of
fulranumab subcutaneous (SC) injections as monotherapy compared with placebo in subjects with signs
and symptoms of osteoarthritis of the hip or knee that were not adequately controlled by current pain
therapy and who are planning a joint replacement surgery.

Secondary Objectives
To evaluate the effect of fulranumab on:
* Patient Global Assessment (PGA) (not for US FDA and Health Canada)
* Joint pain using Numerical Rating Scale (NRS)
* Stiffness, sleep, functional status and well-being as measured by the subject
* Additional analgesic medication use
* Pharmacokinetics and immunogenicity of fulranumab

Exploratory Objectives
To investigate the effect of fulranumab on:
* Post-surgery outcome after joint replacement
* Pre-existing hand OA
* Healthcare resource use and productivity
* Biomarker development

Study design

This is a randomized, double-blind, multi-phase, placebo-controlled, parallel-group efficacy, safety, and tolerability study examining, as monotherapy, fulranumab compared to placebo in subjects with signs and symptoms of hip or knee OA that are not adequately controlled by current pain therapy.

Approximately 450 men or women (*18 years of age) will be randomly assigned in a 1:1:1 ratio, ie, 150 subjects to each double-blind treatment group (placebo Q4wk (every 4 weeks), fulranumab 1mgQ4wk,fulranumab 3mgQ4wk). Subjects will be stratified by: study joint type (at least 33% of hip and of knee),baseline body weight group (<85 kg versus *85 kg), and planned or scheduled joint replacement surgery.

The study is a total of 67 weeks in duration. The study includes the following phases: screening phase (3 weeks that includes a 7-day OA analgesic washout period); double-blind treatment phase (16 weeks);post-treatment follow-up phase (up to 48 weeks). Subjects who discontinue from the double-blind phase and who do not enter the post-treatment follow-up phase will be asked to allow limited safety follow-up
lasting up to 24 weeks after the last injection of study drug. The screening phase can be extended to document OA analgesic failure or to verify contraception method if approved by the medical monitor.

Chronic NSAID use and aspirin use (>325 mg/day inclusive of all acetylsalicylic acid containing products) will be prohibited during the double-blind treatment phase and for 16 weeks after the last injection of study drug. Chronic NSAID use of non-selective NSAIDs or selective NSAIDs [COX-2 inhibitors] is defined as use that lasts for a total of >10 days within each 8-week period, >30 days for each 6-month period, or >60 days over 1 year.

Acetaminophen/paracetamol (3,000 mg per day inclusive of all acetaminophen/paracetamol containing products) will be allowed as rescue medication during the washout and the double-blind phase except for 48 hours before each clinic visit if an efficacy assessment will be performed.

If subjects discontinue treatment, they will complete the double-blind treatment phase assessments up to and including the Week 17 visit (except injection site reaction). Following the completion of the double-blind assessments, they will enter the post-treatment and/or limited safety follow-up.

A subject who undergoes a joint replacement surgery will discontinue treatment and be followed for up to 52 weeks in the post-treatment phase that will include up to 24 weeks of post-surgery assessments.

An unblinded Independent Data Monitoring Committee (IDMC) and 2 blinded Independent Adjudication Committees (IAC) will be commissioned for safety oversight.

Intervention

Subjects will receive 4 subcutaneous (SC) injections of study drug during the double-blind treatment
phase. Fulranumab will be administered as a 1 mg or 3 mg dose every 4 weeks by SC injection of 0.25 mL using a prefilled syringe (1 mg [4.0 mg/mL] and 3 mg [12 mg/mL]). Placebo will be administered by SC injection every 4 weeks using a 0.25 mL volume. The SC injection will be
administered into the thigh or abdomen except in the 2-inch area around the navel.

Study burden and risks

Participation in the study could take up to 67 weeks and longer and could involve 11 visits to the clinic. The patient will also be contacted by phone in between the visits. The number of weeks the4 patient will stay in the study is depending on joint replacement surgery or not and at what stage in the study.

The following procedures will be done during the different visits:

3x physical examination, 11x brief neurological examination, 11x vital signs, 1x medical history including medication history, 7x blood draw, discussconception methods, 5x urine sample, 4x pregnancy test (women), 3x ECG, 3x X-rays hips, knees (and shoulders only at ScR), 11x joint assessments, discuss/review e-diary, discuss side effects. Different questionnaires:

- 1x OA-medical history
- 1x failure OA-pain medication
- 1x medical history nervous system
- 1x BDI-II (presence and severity of symptoms of depression)
- 2 times daily through e-diary: Numerical rating scale (NRS) of OA pain
- 1 x carpal tunnel syndrome
- 10x WOMAC (OA pain, stiffness and activity)
- 3x MMSE(thinking, concentration and memory)
- 10x patient global assessment (PGA) (the treatment has affected the OA)
- 8x EQ-5D-5l (quality of life)
-4x Short Form- 36 Health Survey (SF-36) (health status, pain and well-being)
- 5x AUSCAN (only for patients with OA in their hands)
-4x MOS sleep (questions about (quality of) sleep)
- 2x (subject version- Leeds Assessment of Neuropathic Symptoms and Signs) (S-LANSS): to monitor the possible development of neuropathic pain after a joint replacement (only for patients with a joint replacing surgery)

Most common side effects (affects1 or more users out of 10 users): Arthralgia (achy joints), Headache, Upper respiratory tract infection (colds, cough, runny nose)

Common (affects 1 to 9 users out of 100 users): Rapidly progressing osteoarthritis leading to joint replacement, Carpal Tunnel Syndrome, Hypoesthesia/paresthesia, Recurrence of oral ulcers (cold sores), Peripheral edema

Other side effects:
* Injections of fulranumab and blood draw may cause pain, redness, swelling or bruising at the place where the needle goes into the skin. Fainting, and in rare cases infection, may occur. The amount of blood taken is a small amount

per visit.
* X-Ray Risks:
* The total amount of radiation for this study is approximately equivalent to 13-18 months of whole body exposure to natural background radiation.
* The risk associated with such an exposure is considered minimal and is necessary to obtain the research information desired for the study.
* ECG Risk: There is generally no risk with having an ECG. The sticky patches may pull the skin or cause redness or itching

Please also refer to Protoocl, IB and ICFs

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

The major inclusion criteria are:
1) Man or woman at least 18 years of age;
2) Clinical diagnosis of OA of hip or knee based on criteria defined by the American College of Rheumatology and radiographic evidence of OA (Kellgren-Lawrence class *2) of the study joint;
3) Scheduled joint replacement surgery for the study joint *20 weeks after randomization or planning to undergo a joint replacement surgery for the study joint;
4) Must have an unsatisfactory response (inadequate efficacy or poor tolerability) that includes at least one from each of the following 3 classes of oral analgesic medications (acetaminophen/paracetamol, NSAID, and opioid;
5) Moderate to severe pain and functional impairment based on the NRS, WOMAC pain and physical function subscales, and PGA with specific criteria applied to each scale and subscale. Eligibility criteria will be blinded to subjects, investigators, and site staff to reduce error variance, to improve accuracy of treatment estimates, and to avoid inclusion of subjects who cannot provide interpretable data.
6) During treatment and within 24 weeks after the last injection of study drug: if female of childbearing potential, is not pregnant, breast-feeding, or planning to become pregnant, or if male, will not father a child;
Please refer to the protocol section 4.1 (page 42-44) for a complete list of inclusion criteria)

Exclusion criteria

The major exclusion criteria are medical history that suggests:
1) Increased risk of osteonecrosis (ON) or rapidly progressive osteoarthritis (RPOA);
2) Sympathetic dysfunction as defined in the protocol
3)Central nervous system abnormalities as defined in the protocol
4) Peripheral neurological deficits as defined in the protocol
5)Viral infections as defined in the protocol
6)Cardiovascular related conditions as defined in the protocol
7) History of inherited disorders associated with or causing hypercoagulopathy
8) History of malignanies within the past 2 years
9)Uncontrolled diabetes
10) any other chronic pain condition that would interfere with the subject's ability to assess their OA pain (e.g fibromyalgia)
11) Creatinine clearance < 30 mL per minute
12) ALT or AST>- 2.5 times ULN
13) BMI > 39 kg/m2
14) Other as described in the protocol;Please see a complete list of all exclusion criteria in the protocol section 4.2 (page 44-47)

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:	Recruitment stopped
Start date (anticipated):	30-12-2015
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fulranumab
Generic name:	Fulranumab

Ethics review

Approved WMO Date:	14-04-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-06-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	06-08-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2014-002598-13-NL
ClinicalTrials.gov	NCT02289716
CCMO	NL51453.100.15