A Phase 2a Study Evaluating the Safety, Efficacy, and Pharmacodynamic Effects of ABT-981 in Patients with Knee Osteoarthritis

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Primary ObjectiveTo assess the effect of ABT-981 on OA knee pain using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at Week 16 and synovitis/effusion volume of the index knee using quantitative measures and semi-...

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

Summary

ID

NL-OMON41808

Source
ToetsingOnline

Brief title
M13-741

Condition

- Joint disorders

Synonym
ostheoarthritis, pain

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie B.V.

Source(s) of monetary or material Support: AbbVie B.V.

Intervention

Keyword: and IL-1&beta, IL-1&alfa, inhibitor, Osteoarthritis, Pain, Synovitis

Outcome measures

Primary outcome

Efficacy:

The primary efficacy comparisons will be between each of the ABT-981 treatment groups and the placebo treatment group for the primary efficacy measurement.

Safety:

Safety analyses will be carried out using the safety population, which includes all patients who received at least one dose of study drug. Treatment-emergent adverse events and serious adverse events, which include pre- and post-treatment serious adverse events, will be summarized and reported.

Pharmacodynamic:

Assessment of pharmacodynamic effects of ABT-981 on knee osteoarthritis will be explored by measuring several panels of biomarkers, such as MRI imaging biomarkers, biochemistry biomarkers, and clinical biomarkers.

Secondary outcome

Pharmacokinetic:

Individual ABT-981 serum concentrations will be tabulated for each patient and treatment group and summarized with appropriate statistical methods.

Immunogenicity data will be tabulated and summarized as appropriate. Synovial

fluid ABT-981 concentrations will be compared to measurements in serum to

determine the extent of synovial fluid distribution at steady-state.

Biomarkers:

Summary statistics for all biomarkers at baseline and post-treatment time

points, in addition to change from baseline at each time will be provided.

Study description

Background summary

Osteoarthritis (OA) is a joint disorder that involves degeneration of articular cartilage, inflammation of the entire joint as manifested by synovitis, and changes in the subchondral bone. OA is the most common form of arthritis and the number one cause of workforce disability.
The importance of inflammatory elements in OA is increasingly recognized; the role of cytokines and chemokines as the "inflammatory"
mediators that cause inflamed synovial tissue and cartilage in OA have been extensively studied.
Among these inflammatory mediators, Interleukin-1 (IL-1) is identified as the key factor in cartilage and synovium tissue signaling pathways. IL-1 has long been known as the most potent catabolic cytokine and is thought to play a major role in the development and progression of OA both in terms of disease (structural progression) and symptoms (pain and functional deterioration).
IL-1α and IL-1β are 2 structurally distinct cytokines that bind to the IL-1 receptor complex. Both induce structural changes, such as cartilage degradation, bone sclerosis and synovial proliferation, by inducing proteases and proinflammatory cytokines in joints and have also been shown to play a role in OA pain.
ABT-981 is a novel biologic drug candidate targeting IL-1α and IL-1β.

Study objective

Primary Objective
To assess the effect of ABT-981 on OA knee pain using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at Week 16 and synovitis/effusion volume of the index knee using quantitative measures and semi-quantitative MRI scoring at Week 26.

Secondary Objectives
* To evaluate the safety and tolerability of ABT-981 in patients with knee OA.
* To evaluate the effect of ABT-981 on physical function scores of the index knee at Weeks 16, 26 and 52 using WOMAC.
* To evaluate the effect of ABT-981 on index knee pain scores at Weeks 26 and 52 using WOMAC.
* To evaluate the effect of ABT-981 in reduction of bone marrow lesions (BML) of the index knee MRI at Weeks 26 and 52 using semi-quantitative measurements (WORMS).
* To evaluate the effect of ABT-981 on index knee resting pain at Weeks 16, 26 and 52 using the Intermittent and Constant Osteoarthritis Pain (ICOAP) score.
* To evaluate the effect of ABT-981 on index knee resting pain at Weeks 16, 26 and 52 using the 11-point NRS scale (NRS-11).
* To evaluate the effect of ABT-981 on Patient Global Assessment of Arthritis at Weeks 16, 26 and 52.
* To evaluate the effect of ABT-981 on the preservation of cartilage volume/thickness of the index knee using MRI at Weeks 26 and 52.

Exploratory Objectives
* To evaluate the effect of ABT-981 on index knee joint structure using semi-quantitative global assessment MRI scoring method (WORMS) at Weeks 26 and 52.
* To evaluate the effect of ABT-981 on Outcome Measures in Rheumatology Clinical Trials/Osteoarthritis Research Society International (OMERACT/OARSI) responder criteria at Weeks 16, 26 and 52.
* To evaluate the effect of ABT-981 on synovitis and effusion volume of the index knee MRI at Week 52.
* To evaluate the effect of ABT-981 on index knee joint stiffness using WOMAC at Weeks 16, 26 and 52.
* To evaluate rescue medication use between treatment groups and control group.
* To evaluate the effect of ABT-981 on joint space width of the index knee using X-ray at Week 52.
* To explore the pharmacokinetics (PK) and pharmacodynamics (PDyn) relationship of ABT-981 using imaging and non-imaging biomarkers, as well as clinical outcomes.
* To evaluate several panels of serum/plasma, urine and synovial fluid biomarkers at various time points for use in further development of ABT-981.

Study design

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the safety, tolerability, efficacy and pharmacodynamic effects of ABT-981 in patients diagnosed with osteoarthritis of the knee. Approximately 320 (~80 per group) patients meeting all of the inclusion criteria and none of the exclusion criteria during Screening (within 45 days prior to the first dose of study drug) will be enrolled. Patients taking analgesics must complete a Washout

Period and discontinue all analgesic medications for at least 5 half-lives of the longest acting analgesic used, or 48 hours, whichever is longer, prior to the first dose of study drug. Patients will be permitted to take acetaminophen (paracetamol) as rescue mediation during the Washout Period through Week 26 MRI exam. Between week 16 and week 26 ibuprofen can also be given additionally. After the Week 26 MRI exam, patients will be allowed to resume approved oral standard of care medications. Patients will be randomized to one of the four treatment groups to receive either ABT-981 or placebo for 50 weeks (treatment period).

Intervention

Approximately 320 (~80 per group) patients meeting all of the inclusion criteria and none of the exclusion criteria during Screening (within 45 days prior to the first dose of study drug) will be enrolled. Patients taking analgesics must complete a Washout Period and discontinue all analgesic medications for at least 5 half-lives of the longest acting analgesic used, or 48 hours, whichever is longer, prior to the first dose of study drug. Patients will be permitted to take acetaminophen (paracetamol) as rescue mediation during the Washout Period through Week 26 MRI exam. After the Week 26 MRI exam, patients will be allowed to resume approved oral standard of care medications. Patients will be randomized to one of the four treatment groups to receive either 25, 100, 200 mg ABT-981, or placebo for 50 weeks (treatment period). Patients will undergo an ultrasound, 2 X-rays and 3 MRIs during the study.

Study burden and risks

The risks associated with this study are linked together with the possible side effects of the investigational product. The burden of the subject will continue to work with the study procedures, visits, and venapunctions. All subjects will be closely monitored and supervised by experienced doctors and study staff for possible side effects.

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.Subject must have radiographic evidence of knee osteoarthritis in the medial compartment of the index knee with Kellgren-Lawrence Grade 2 or 3 (with minimum 2 mm joint space width) during Screening as evaluated by a qualified central imaging reader. Prior radiographs taken
no more than 3 months before Study Day 1 with Synaflexer* can be submitted for centralized eligibility reading.
2. Subject must have either constant or intermittent index knee pain at least 14 days (regardless of the intensity) over the past 30 days at the initial screening visit. The intensity of index knee pain is between 4 and 8, inclusive, at the initial Screening Visit and Study Day 1 (as recorded on Question 1 of the Index Knee Pain Intensity Questionnaire).
3.Subject has one or more clinical signs and symptoms of active inflammation in the index knee as defined by (but not limited to) localized pain, joint stiffness, swelling and effusion during Screening Period and Study Day 1.
4.Presence of synovitis in the index knee confirmed either by ultrasound or MRI during Screening.
5.Subject discontinued analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and nutraceuticals (e.g., glucosamine, chondroitin sulfate, shark cartilage, diacerein, soy extract). The washout period will be at least 5 half-lives of the longest acting analgesic used, or 48 hours, whichever is longer prior to first dose of study drug.

Exclusion criteria

1.History of major allergic reaction or significant sensitivity to any constituents of the study

drug; or history of anaphylactic reaction to any agent (e.g., food products or bee stings) or history of a major reaction to any Immunoglobulin G (IgG) containing product.
2.Significant trauma or surgery to the index knee within the last year or arthroscopy of the index knee within 6 months of the initial Screening Visit.
3.Kellgren-Lawrence Grade 1 or 4 in the index knee.
4.Severe knee malalignment, either greater than 4.0° in varus; or greater than 8.0° in valgus angulation in the index knee.
5.Diagnosis of one or more of the following:
a.Inflammatory arthritis such as rheumatoid arthritis, autoimmune disorder, seronegative spondyloarthropathy, gout, or pseudogout (defined as acute episodic attacks of swollen , painful joints in a subject with X-Ray chondrocalcinosis or CPPD crystals);
b.Other chronic painful syndromes (such as Paget's disease and fibromyalgia) and clinically significant non-articular musculoskeletal pain that could interfere with assessment of pain at the index knee.
6. History or evidence of active tuberculosis (TB)
7. Any uncontrolled medical illness or unstable treatment.

Study design

Design

Study phase:	2
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):	06-10-2015
Enrollment:	17
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	ABT-981
Generic name:	ABT-981
Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo

Ethics review

Approved WMO Date:	15-05-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-08-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-09-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-11-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-12-2014
Application type:	Amendment

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	04-06-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-08-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-01-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2013-003467-60-NL
ClinicalTrials.gov	NCT01668511
CCMO	NL48135.058.14