A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN THE TREATMENT OF ACTIVE ANKYLOSING SPONDYLITIS

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• Primary ObjectiveTo evaluate the efficacy of apremilast 30 mg twice a day (BID), compared with placebo, in the reduction of signs and symptoms in subjects with active AS at 16 weeks of treatment.• Secondary Objectives- To evaluate the efficacy of...

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

Summary

ID

NL-OMON37830

Source
ToetsingOnline

Brief title
CC-10004-CL-01 AS

Condition

- Joint disorders

Synonym
Bekhterev's disease, Chronic inflammatory disease of the axial skeleton

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Ankylosing spondylitis, apremilast, efficacy, safety

Outcome measures

Primary outcome

The primary endpoint will be the proportion of subjects who achieve an ASAS 20

at Week 16. The ASAS is the Assessment of SpondyloArthritis international

Society (see Section 10.1.1 for ASAS response definitions). The ASAS 20 is

defined as achieving:

• An improvement from baseline of >= 20% and >= 1 unit in at least three of the

four ASAS domains on a scale of 0 to 10 units, and

• No worsening from baseline of >= 20% and >= 1 unit in the remaining ASAS domain

on a scale of 0 to 10 units.

The four ASAS domains are:

1. Patient Global Assessment of Disease (0 to 10 unit NRS);

2. Total Back Pain NRS;

3. Function (the Bath Ankylosing Spondylitis Functional Index [BASFI] score

NRS);

4. Inflammation (mean of the two Bath Ankylosing Spondylitis Disease Activity

Index [BASDAI] NRS Questions #5 and #6 for morning stiffness).

Secondary outcome

Secondary Endpoints

• Change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI)

at Week 24

(for the comparison between apremilast 30 mg BID and placebo)

• Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index

(BASDAI) at Week 24

(for the comparison between apremilast 30 mg BID and placebo)

• Proportion of subjects achieving an ASAS 20 at Week 24

(for the comparison between apremilast 30 mg BID and placebo)

• Change from baseline in the physical component score of the Medical Outcome

Study Short Form 36-Item Health Survey (SF-36) scale at Week 24

(for the comparison between apremilast 30 mg BID and placebo)

• Change from baseline in Bath Ankylosing Spondylitis Metrology Index -Linear

(BASMI-Linear) at Week 24

(for the comparison between apremilast 30 mg BID and placebo)

• Change from baseline in BASFI at Week 24

(for the comparison between apremilast 20 mg BID and placebo)

• Change from baseline in BASDAI at Week 24

(for the comparison between apremilast 20 mg BID and placebo)

• Proportion of subjects achieving an ASAS 20 at Week 24

(for the comparison between apremilast 20 mg BID and placebo)

• Change from baseline in the physical component score of the SF-36 scale at

Week 24

(for the comparison between apremilast 20 mg BID and placebo)

• Change from baseline in BASMI-Linear at Week 24

(for the comparison between apremilast 20 mg BID and placebo)

• Change from baseline in the radiographic score using the modified Stoke

Ankylosing Spondylitis Spine Score (m-SASSS) at Week 104 (Year 2) and Week 260

(Year 5) by treatment group (20 mg BID, 30 mg BID, Placebo/30 mg BID, 20 mg

BID/30 mg BID)

Study description

Background summary

Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown etiology that belongs to a group of disorders collectively termed spondyloarthropathies (Davis, 2007). Among the spondyloarthropathies, four major clinical syndromes are recognized: AS, psoriatic arthritis (PsA), enteropathic arthritis, and reactive arthritis (formerly Reiter's syndrome).
The spondyloarthropathies are distinguished from rheumatoid arthritis by their seronegativity for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies; predilection for spinal, sacroiliac and entheseal involvement; and the tendency of peripheral joint involvement to reflect a predilection for the lower extremities, with few joints involved in an asymmetrical fashion.
Extra-articular features of the spondyloarthropathies also contrast with rheumatoid arthritis, especially with regard to skin (psoriasis, keratoderma blenorrhagica, and circinate balanitis), cardiac (aortitis, aortic valve insufficiency), mucus membrane (colitis, urethritis, oral ulcers) and inflammatory eye involvement (anterior uveitis). The histocompatibility antigen, Human Leukocyte Antigen B27 (HLA-B27) is also strongly linked with the presence of spondyloarthropathies, particularly AS.
Apremilast (CC-10004) is a novel, orally available small molecule that specifically inhibits phosphodiesterase type 4 (PDE4), which increases intracellular cyclic adenosine monophosphate (cAMP). This increase in cellular cAMP modulates multiple pro-inflammatory and anti-inflammatory mediators.

Apremilast is currently being developed for use in the treatment of immune-mediated inflammatory conditions such as psoriatic arthritis (PsA), psoriasis, rheumatoid arthritis (RA), Behçet disease (BD), and AS.

Study objective

• Primary Objective
To evaluate the efficacy of apremilast 30 mg twice a day (BID), compared with placebo, in the reduction of signs and symptoms in subjects with active AS at 16 weeks of treatment.

• Secondary Objectives
- To evaluate the efficacy of apremilast 30 mg BID, compared with placebo, in the reduction of signs and symptoms, improvement in physical function and range of motion in subjects with active AS at 24 weeks of treatment.
- To evaluate the efficacy of apremilast 20 mg BID, compared with placebo, in the reduction of signs and symptoms, improvement in physical function and range of motion in subjects with active AS at 24 weeks of treatment.
- To evaluate the efficacy of two doses of apremilast (30 mg BID and 20 mg BID) on AS lesions in the cervical and lumbar spine as assessed by radiographs in subjects with active AS at 104 Weeks and 260 Weeks of treatment.
• Safety Objectives
- To evaluate the safety and tolerability of two doses of apremilast (30 mg BID and 20 mg BID), compared with placebo, in subjects with active AS for up to 24 weeks of treatment.
- To evaluate the long-term safety and tolerability of two doses of apremilast (30 mg BID and 20 mg BID) in subjects with active AS for up to 5 years of treatment.
• Exploratory Pharmacokinetic and Pharmacodynamic Objectives
- To explore and characterize the population pharmacokinetics (PK) of apremilast in a subset of subjects with active AS.
- To explore and evaluate the relationship between the exposure of apremilast and pharmacodynamic (PD) and clinical outcomes in a subset of subjects with active AS for up to 24 weeks.
- To understand the mechanism of apremilast pharmacological activity in a subset of subjects with active AS, as measured by changes in soluble markers of inflammation and bone turnover in the serum or plasma.
• Exploratory Clinical Objectives
- To explore the efficacy of two doses of apremilast (30 mg BID and 20 mg BID), compared with placebo, on the quality of life in subjects with active AS for up to 24 weeks of treatment.
- To explore the efficacy of two doses of apremilast (30 mg BID and 20 mg BID) for up to 5 years for:
a. Signs and symptoms;
b. Physical function;
c. Range of motion;

d. Quality of life.
• Exploratory Pharmacogenetic Objective
- To explore pharmacogenetic (PG) markers associated with clinical response to two doses of apremilast (30 mg BID and 20 mg BID), compared with placebo, in a subset of subjects with active AS.
• Exploratory Imaging Objectives
- To explore the efficacy of two doses of apremilast (30 mg BID and 20 mg BID) on AS lesions in the spine as assessed by magnetic resonance imaging (MRI) in a subset of subjects with active AS at Week 16 (placebo-controlled), Week 52, Week 104 and Week 260.

Study design

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety study.

Intervention

Approximately 456 subjects with active AS will be enrolled and randomized in a 1:1:1 ratio to receive oral (PO) administration of apremilast 30 mg BID, apremilast 20 mg BID, or placebo for 24 weeks followed by a long-term extension.

Study burden and risks

Zie de flowcharts of the protocol version 20Mar2012 page 41 t/m 48.

Summary of procedures:
7x Chest Radiograph
3x ECG
4x Pregnancy test
3x Radiograph (spine)
25x Vital signs
17x Physical exam
19x Clinical laboratory tests
17x Questionnaires (number of visits in the complete study where the patients needs to complete questionnaires)

Side effects Apremilast:
As of 31 March 2012, Apremilast has been given to about 4471 subjects. The most frequent risks, discomforts and side effects in subjects that have taken apremilast: headache, stuffiness or infections of the nose and throat (upper respiratory tract infections), feeling tired, stomach pain or discomfort, nausea, vomiting and diarrhea. Most of these side effects were mild to moderate in intensity. They stopped with continued treatment or shortly after the study drug was stopped. Similar side effects have been observed in studies that are

running now.

Because apremilast also blocks some factors in the body that fight infections, it is possible you could more easily get infections.
It is possible that the condition for which you are being treated may worsen during the study.

The risks of blood sampling are: fainting, bleeding, bruising, discomfort, dizziness, infection and/or pain at the point of puncture site.
The risks of X-rays are: during X-ray assessments high energy of the radiation may possibly damage a very small amount of your body's cells. The risk of getting cancer from x-rays is very small. With 300 medical x-rays in a year, it would increase the chances of getting cancer by only 1%.
The risks of pregnancy: the risks to an unborn child (fetus) or nursing child from apremilast are not known at this time. Women should not become pregnant or lactating during the study participation due to the potential risk to an unborn child. The partner should not become pregnant during your study participation.

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. Must have a documented diagnosis of ankylosing spondylitis as defined by low back pain and stiffness, which improves with exercise, but is not relieved by rest for more than 3 months prior to screening. At the completion of screening procedures, a documented diagnosis of definite active AS, as defined by the modified New York criteria (1984) whereby both criteria, at least 1 radiographic criterion and at least 1 clinical criterion, must be met (Appendix A of the protocol):
a. Radiographic criteria (at least 1), documented by the central reader before the subject is randomized:
i. Sacroiliitis Grade >= 2 bilaterally, or
ii. Sacroiliitis Grade 3 to 4 unilaterally
b. Clinical criteria (at least 1), documented in physical examination:
i. Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest
ii. Limitation of motion of the lumbar spine in both the sagittal and frontal planes
iii. Limitation of chest expansion relative to normal values corrected for age and gender
2. Must have symptoms of active axial disease at screening and baseline (at time of randomization), as determined by a BASDAI NRS score of >= 4 and a total back pain NRS score >= 4.
3. Must be receiving treatment on an outpatient basis.
4. Must be in good health (except for AS) as judged by the Investigator, based on medical history, physical examination, 12-lead ECG, chest radiograph, clinical laboratories and urinalysis.
5.,Must agree to maintain the same stable dose of medication (or lack of medication) taken for AS prior to randomization through Week 24 of the study as described below. Change in medication may be allowed for safety reasons (See Section 9.1 of the protocol).
a. Analgesics must be stable for at least 14 days prior to Day 0
i. Non-investigational NSAIDs and/or COX-2 inhibitors
ii. Acetaminophen/paracetamol <= 2600 mg/day
iii. Opioid analgesics <= 30 mg oral morphine or equivalent per day
b. Disease-modifying anti-rheumatic drugs (DMARDs) must have been taken for at least 16 weeks and must be stable for at least 28 days prior to Day 0 within the following doses:
i. Methotrexate: oral <= 25 mg/week; parenteral <= 25 mg/week
Note: Supplemental oral folate (folic acid) is required with a minimum dose of 5 mg/week, or oral leucovorin up to 10 mg/week for subjects taking methotrexate).
ii. Sulfasalazine <= 3 g/day
iii. Hydroxychloroquine <= 400 mg/day; Chloroquine <= 250 mg/day
Note: Regular safety monitoring, particularly eye exams must be conducted according to

local practice guideline for subjects on hydroxychloroquine or chloroquine.
c. Corticosteroids (prednisone <= 10 mg/day or prednisone-equivalent) must be stable for at least 28 days prior to Day 0.
6. Must meet the following laboratory criteria at screening:
a. White blood cell count >= 3000/mm3 (>= 3.0 x 109/L) and < 14,000/mm3 (< 14 x 109/L)
b. Platelet count >= 100,000/µL (>= 100 x 109/L)
c. Serum creatinine <= 1.5 mg/dL (<= 132.6 µmol/L)
d. AST (SGOT) and ALT (SGPT) <= 2 x upper limit of normal (ULN). If initial test shows ALT or AST > 2 times the ULN, one repeat test is allowed during the screening period.
e. Total bilirubin <= 2 mg/dL (<= 34 µmol/L). If initial test result is > 2 mg/dL, one repeat test is allowed during the screening period.
f. Hemoglobin >= 9 g/dL (>= 5.6 mmol/L)
g. Hemoglobin A1c <= 9.0%
h. Negative for hepatitis B surface antigen
i. Negative for hepatitis C antibody

Exclusion criteria

1. Major surgery (including spinal surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization.
2. Autoimmune diseases such as, but not limited to: systemic lupus erythematosus, mixed connective tissue disease, multiple sclerosis, or scleroderma.
3. Prior history of, or current, inflammatory joint disease other than AS (eg, rheumatoid arthritis, gout, reactive arthritis, psoriatic arthritis, Lyme disease).
4. Uncontrolled, severe psoriasis (defined as Body Surface Area > 10%) or active inflammatory bowel disease (Crohn*s disease or ulcerative colitis) based on an unequivocal positive calprotectin stool test defined by the local or central lab reference values.
5. Uncontrolled uveitis at the time of randomization. Asymptomatic, concurrently treated and controlled uveitis is acceptable at randomization, as long as the treatment is limited to topical ophthalmic therapy and/or intra-ocular injections of corticosteroids. Subjects are allowed to be initiated with these therapies during screening, continue on them through randomization and tapered off or discontinue these therapies while on study as medically appropriate. Systemic treatment for uveitis is not allowed, and would result in discontinuation from the study.
6. Prior treatment with a TNF blocker or any biologic treatment for AS.
7. If discontinuing treatment of DMARD, then adequate washout is required prior to randomization (See separate sheet of List of DMARD Washout Periods).
8. Treatment with any investigational agent within four weeks (or five half-lives of the investigational drug, whichever is longer) of screening.
9. Intra-articular or parenteral corticosteroids are not allowed within 6 weeks prior to randomization.
10. Any previous treatment with alkylating agents such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation.

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):	15-07-2013
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	apremilast
Generic name:	apremilast

Ethics review

Approved WMO Date:	15-05-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-12-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-12-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-02-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-02-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-11-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-10-2014

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-05-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-05-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-06-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-06-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-06-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	10-01-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2011-001555-37-NL
ClinicalTrials.gov	NCT01583374
CCMO	NL40499.068.12

Study results

Results posted: 09-09-2019

First publication
17-06-2019