MULTICENTER STUDY WITH A 16-WEEK DOUBLE-BLIND, PLACEBO-CONTROLLED (DURING THE INITIAL 2 WEEKS) RANDOMIZED PERIOD, FOLLOWED BY A 24-WEEK OPEN LABEL EXTENSION TO ASSESS MAGNETIC RESONANCE IMAGE-VERIFIED EARLY RESPONSE TO CERTOLIZUMAB PEGOL IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS

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

Summary

ID

NL-OMON34044

Source
ToetsingOnline

Brief title
MARVELOUS

Condition

- Joint disorders

Synonym
arthritis, Rheumatoid Arthritis

Research involving
Human

Sponsors and support

Primary sponsor: UCB Pharma
Source(s) of monetary or material Support: UCB Pharma

Intervention

Keyword: Active Rheumatoid arthritis, Certolizumab Pegol, Early response, Magnetic Resonance Imaging

Outcome measures

Primary outcome

Change from Baseline (Day 0) in OMERACT RAMRIS synovitis score measured with

MRI (gadolinium-containing contrast agent) of one hand and wrist at Days 7, 14,

28, and Weeks 8 and 16.

Secondary outcome

• Dynamic MRI parameters of IRE, maximal enhancement (E Max), and time of onset

of enhancement (Tonset) at Days 0, 7, 14, 28 and Weeks 8 and 16.

• Correlation of reduction of synovitis as measured by MRI at Week 16 with:

* EULAR response

* ACRp response

* DAS 28 response

* Early changes in hand bone mineral density as measured by DXR

Study description

Background summary

MRI is the only noninvasive technique that allows simultaneous assessment of all the components of the diarthrodial joint, including synovia, cartilage, and bone, without using radiation. There are validated criteria for both the activity of the synovitis, and destructive changes (Lassere et al, 2003). The OMERACT RAMRIS (RA-MRI Scoring) system assesses bone erosions, bone oedema, and synovitis. In OMERACT RAMRIS, the synovitis is assessed as the maximal enhancement of the synovia after infusing Gadolinium-containing contrast agent.

In addition to RAMRIS, a relative early enhancement rate (RER) can be measured. This is dependent on the synovial vascularity and the capillary permeability, which are sensitive to the changes in the inflammatory activity. Thus, the early enhancement rate offers a rapidly responding and accurate technique to assess the changes in the synovial inflammation.
RER correlate well with the joint pain, ESR, and the erosive progression (Huang J et al 2000). The enhancement rate measurements also have a good inter-reader/inter-scan reproducibility (Lassere et al 2003). However, the measure depends on the precise imaging technique and equipment (Hodgon RJ et al, 2008). This is why we will use only 3 MRI facilities, and the same person will take care of the standardization of the measurement techniques and protocols.

Earlier studies have shown 25% to 40% changes in the dynamic MRI measures of arthritis by 16 weeks of Abatacept therapy (Rosengren S et al., 2008). The largest change was in the initial (early) rate of enhancement. However, no study has looked for the earliest time point, when the biological or DMARD therapy starts to affect the inflammatory process in the synovia. Certolizumab pegol (CZP) is an ideal agent to study the issue, since clinical response is observed as early as 1 week following initiation of CZP therapy.

Study objective

The purpose of this study is to identify the first time-point the OMERACT RAMRIS score for the activity of synovitis is statistically significantly reduced compared to Baseline, in response to cerolizumab pegol (CZP) therapy. In addition, the early enhancement rate starting 7 days after Baseline will be measured. This will provide valuable information on the kinetics of the CZP, and help to guide future trials.

Further, the efficacy of CZP will be examined with regards to bone edema and bone erosion to further characterize the process of bone erosion.

Further, to evaluate the tolerability and safety of CZP therapy.

Study design

This is a Phase 3b multicenter, randomized, double-blind, placebo-controlled study. Eligible patients will be randomized (2:1 ratio) to receive either:
• CZP 400mg at Weeks 0, 2 and 4, followed by 200mg and placebo at Week 6 and 200mg at Weeks 8, 10, 12, 14, and 16,
• or placebo at Day 0 (2 injections) and then CZP 400mg at Weeks 2, 4 and 6 followed by 200mg at Weeks 8, 10, 12, 14 and 16.

The study population will consist of subjects with a diagnosis of adult-onset RA of at least 3 months duration but not longer than 15 years as defined by the 1987 American College of Rheumatology classification criteria. In addition, subjects must be on DMARD therapy for at least 12 weeks with a dose and route of administration stable for at least 8 weeks prior to Baseline. Subjects are allowed to continue their current nonbiological treatment regimens for RA, if the regimens are not modified during the double-blind study period (16 weeks). The oral corticosteroid prednisone (<=10mg per day) is permitted if the dose regimen and/or the route of administration is not changed in the 28 days prior to Baseline.

After Week 16, patients will be given the opportunity to enter the open-label phase and receive 200mg every 2 weeks CZP free of charge for 6 months.

Intervention

• CZP 400mg at Weeks 0, 2 and 4, followed by 200mg and placebo at Week 6 and 200mg at Weeks 8, 10, 12, 14, and 16,
• or placebo at Day 0 (2 injections) and then CZP 400mg at Weeks 2, 4 and 6 followed by 200mg at Weeks 8, 10, 12, 14 and 16.

The study duration per subject will be approximately 14 months including a 1-month Screening Period, a 4-month double-blind period (including an initial 2 week placebo controlled period), a 6-month open-label period, and a 2.5 month Safety Follow-Up Period with a Safety Follow-Up phone contact performed 10 weeks after the last dose of study drug administration.
The end of the study is defined as the date of the last Safety Follow-Up phone contact of the last subject in the study.

Study burden and risks

Benefits:
During the study the general health of the subjects will be closely monitored and the study medication will be provided for free by UCB during participation in this study.

The subject may benefit from the effects of the study drug (certolizumab pegol) on their symptoms. The information gathered during the study will help researchers to find out if certolizumab pegol will help other people with rheumatoid arthritis.
MRI information collected during the study may also help researchers to assess the rapid onset of response to certolizumab pegol after the first administration.

Burden and Risks:

Based on the clinical studies data, more than 5,100 subjects (including at least 126 healthy volunteers, 117 subjects with psoriasis, 2,511 subjects with Crohn*s disease and 2,367 subjects with rheumatoid arthritis) have received at least one dose of certolizumab pegol (the study drug). These patients have received either the freeze-dried (powder) form of the drug, which was mixed with liquid before injection or the liquid form of the drug. Certolizumab pegol has been found to be generally well tolerated and have an acceptable safety profile as a TNF inhibitor. Side-effects that have been found to be more common in rheumatoid arthritis subjects who took certolizumab pegol than those who took placebo are: infections (such as lung, urine, and throat; bacterial and viral), headaches, hypertension (high blood pressure), back pain, rash, fever, elevated liver enzymes, and fatigue (feeling tired). Other more serious side effects resulting in hospitalizations or death also have occurred in patients taking certolizumab pegol.

Serious side effects:

Treatments that block TNF (tumor necrosis factor) might reduce the body*s ability to fight infection. Subjects participating in studies with certolizumab pegol (the study drug) may have an increased risk of developing infections, some of which have been serious or fatal (causing death). Many of the serious infections have occurred in subjects taking other immunosuppressant medications such as methotrexate, azathioprine, or corticosteroids. Some serious infections that have occurred in patients taking certolizumab pegol include tuberculosis, sepsis (serious infection of the blood), pneumonia and pyelonephritis (kidney infection). However, not all infections were thought to be related to the study treatment by the doctor.

The use of TNF blockers such as certolizumab pegol also may increase the risk for getting active tuberculosis.

Invasive opportunistic fungal (yeast and mold) infections like histoplasmosis (infection with Histoplasma capsulatum fungus), coccidioidomycosis (infection with Coccidioides immitis fungus), paracoccidioidomycosis (infection with Paracoccidioides brasiliensis fungus), aspergillosis (infection with

Aspergillus fumigatus fungus) and pneumocystosis (infection with Pneumocystis jiroveci fungus) can possibly develop in subjects who are taking drugs that block TNF like certolizumab pegol.

The US Food and Drug Administration (FDA) has issued a warning that certain types of cancers called lymphoma and leukemia have been reported in patients taking TNF blockers.

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. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent is signed and dated by the subject or by the parent(s) or legal

representative.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule or medication intake according to the judgment of the Investigator.
3. Subjects must be at least 18 years old at the Screening Visit.
4. Female subjects must be either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (either oral/parenteral/implantable hormonal contraceptives, intrauterine device, or barrier and spermicide). Abstinence only is not an acceptable method. Subjects must agree to use adequate contraception during the study and for 10 weeks after their last dose of CZP (or longer if required by local regulations).
5. Subjects must have a diagnosis of adult-onset RA of at least 3 months duration but not longer than 15 years as defined by the 1987 American College of Rheumatology classification criteria.
6. Subjects must be rheumatoid factor positive and/or anti-CCP positive.
7. Subjects must have active RA disease as defined by:
• >=1 tender joints and >=1 swollen joints (at Baseline) in the joint area imaged which is 1 wrist and hand (MCP2-5); and
• >=3 tender joints (28 joint count) at Baseline; and
• >=3 swollen joints (28 joint count) at Baseline.
8. Subjects must be on DMARD therapy for at least 12 weeks and the dose and route of administration should be stable for at least 8 weeks prior to Baseline.
9. Subjects must be able and willing to comply with the requirements of the study protocol.
10. Subjects must have creatinine within normal limits during the 4 weeks prior to Baseline.

Exclusion criteria

1. Subject has previously participated in this study or subject has previously been assigned to treatment in a study of the medication under investigation in this study.
2. Subject has a history of chronic alcohol or drug abuse within the last insert timeframe (eg, 6 months).
3. Subject has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject*s ability to participate in this study.
4. Subject has a known hypersensitivity to any components of the IMP as stated in this protocol.;RA Disease-Related Exclusions:
5. Subjects must not have a secondary, noninflammatory type of musculoskeletal condition (eg, osteoarthritis or fibromyalgia) that in the Investigator*s opinion is symptomatic enough to interfere with evaluation of the effect of study drug on the subject*s primary diagnosis of RA.
6. Subjects must not have a diagnosis of any other inflammatory arthritis (eg, psoriatic arthritis or ankylosing spondylitis).
7. Subjects must not have a history of an infected joint prosthesis at any time with that prosthesis still in situ.
8. Subjects must not have received any of the prohibited medication as detailed in the following table: See table 6.1 prohibited medication protocol page 30

9. Subjects must not have received any experimental nonbiological therapy in the 3 months or within 5 half-lives prior to Baseline (whichever is longer).
10. Subjects must not have received any experimental biological agent in the past 3 months or within 5 half-lives prior to Baseline (whichever is longer).
11. Subjects must not have received infliximab or abatacept therapy in the 3 months prior to Baseline.
12. Subjects must not have received adalimumab, golimumab or etanercept therapy in the 2 months prior to Baseline.
13. Subjects must not have received treatment with rituximab.
14. Subjects must not have received more than 1 biological agent.
15. Subjects must not have been primary failures (ie, never achieved meaningful improvement) to prior anti-TNF therapy.
16. Subjects must not have contraindications for MRI and contrast agent.;Medical History Exclusion:
17. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the trial or within 12 weeks following last dose of study drug.
18. Subjects with a history of chronic infection (more than 4 episodes requiring antibiotics/antivirals during the preceding year), recent serious or life-threatening infection within 6 months (including herpes zoster), or any current sign or symptom that may indicate an infection.
19. Known TB disease, high risk of acquiring TB infection, or latent TB infection:
a. Known TB disease
• Currently active TB disease or clinical signs and symptoms suspicious for TB.
• Prior history of active TB disease involving any organ system (clinically documented).
• Chest radiograph evidence of past active TB disease (not clinically documented), which could include apical lung fibrosis, pleural thickening, calcified lung nodules, calcified hilar lymph nodes, pericardial calcification.
b. High risk of acquiring TB infection
• Known exposure to another person with active TB disease <3 months prior to Screening.
• High risk of future exposure to another person with active TB disease:
1. Time spent in a health care delivery setting.
2. Time spent in an institutional setting.
c. Latent TB infection - Subjects who don*t meet criteria *a* or *b* but do meet any of the following, regardless of prior TB treatment:
• Current PPD positive (+) (test must be performed <=3 months prior to Screening)
or
• Previously documented history of a severe positive PPD reaction (test performed >3 months prior to Screening) and
1. Elispot (performed <=3 months prior to Screening) positive or indeterminate or
2. QuantiFERON (performed <=3 months prior to Screening, only if Elispot unavailable) positive or indeterminate.
• Subjects with no documented history of a severe positive PPD test can only receive the PPD test for Screening.
• Exception from exclusion *1c* is permitted only if treatment for latent TB infection is initiated or has been initiated at least 1 month prior to study drug administration and treatment is still ongoing at time of study entry.
• A positive PPD is defined as >=5mm of induration 48 to 72 hours after intradermal injection

of 5TU of PPD-S or 2TU of PPD-RT23 regardless of the subject*s history of BCG vaccination.
• Reports of PPD results not taken at Screening but (performed <=3 months prior to Baseline and) reported from elsewhere must be documented with exact induration measurement.
• Treatment for latent TB infection includes eg, isonicotinic acid hydrazide/isoniazid (INH) therapy for 9 months (with vitamin B6); another latent TB infection treatment regimen should be considered if the subject is living in or has emigrated recently from a country with a high endemic rate of INH*resistant or multi-drug resistant TB.
20. Subjects at a high risk of infection (eg, leg ulcers, indwelling urinary catheter and persistent or recurrent chest infections and subjects who are permanently bedridden or wheelchair bound).
21. Subjects with a history of a lymphoproliferative disorder including lymphoma or signs and symptoms suggestive of lymphoproliferative disease.
22. Subjects with concurrent acute or chronic viral hepatitis B or C.
23. Subjects with known human immunodeficiency virus (HIV) infection.
24. Subjects receiving live or attenuated vaccination within 8 weeks prior to Baseline (eg, inactivated parenteral influenza and pneumococcal vaccines are allowed, but nasal influenza vaccine is not).
25. Concurrent malignancy or a history of malignancy (other than carcinoma of the cervix or basal cell carcinoma successfully treated more than 5 years prior to Screening).
26. Subjects with a current or recent history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological or cerebral disease.
27. Subjects with class III or IV congestive heart failure according to the New York Heart Association (NYHA) 1964 classification criteria.
28. Subjects with a history of, or suspected, demyelinating disease of the central nervous system (eg, multiple sclerosis or optic neuritis).
29. Subjects with any other condition (eg, clinically significant laboratory values) which in the Investigator*s judgment would make the subject unsuitable for inclusion in the study.

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):	15-12-2011
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cimzia®
Generic name:	Certolizumab pegol
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-09-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-12-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-04-2011
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-05-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-06-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	26-10-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2009-013758-33-NL
CCMO	NL33243.091.10