A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CERTOLIZUMAB PEGOL IN COMBINATION WITH METHOTREXATE FOR INDUCING AND SUSTAINING CLINICAL RESPONSE IN THE TREATMENT OF DMARD-NAÏVE ADULTS WITH EARLY ACTIVE RHEUMATOID ARTHRITIS

Published: 05-03-2012
Last updated: 26-04-2024

The study has the following 3 main objectives pertaining to the treatment of DMARD-naïve subjects with adult-onset, early, active, RA, diagnosed within 1 year before Screening using the 2010 ACR/EULAR RA classification criteria:1.To show that...

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

Summary

ID

NL-OMON37680

Source
ToetsingOnline

Brief title
RA0055

Condition

- Immune disorders NEC

Synonym
Early phase Rheumatoide Artritis, Rheumtoide Arteritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Certolizumab, DMAR naive, Early Rheumatoide arteritis, Metotrexate

Outcome measures

Primary outcome

Period1 ; primary efficacy variable is the proportion of subjects in sustained

remission (defined as DAS28[ESR] <2.6 at Week 40 and Week 52 visits) at Week 52

Period 2 ; primary efficacy variable is the proportion of subjects who maintain

LDA (DAS28[ESR] *3.2) from Week 52 through Week 104 without flaring.

Secondary outcome

Period 1 ; key secondary efficacy variable is: The proportion of subjects in

sustained LDA (defined as DAS28[ESR] *3.2 at Week 40 and Week 52 visits) at

Week 52.

Radiographic, Clinical and Patient reported variables will be assessed from

Baseline to Week 52 - for details see page 22-24 of the protocol

Periode 2 ; key secondary efficacy variable is the proportion of subjects who

are in sustained remission at Week 52 and maintain their remission (DAS28[ESR]

<2.6) from Week 52 through Week 104 without flaring

Radiographicm, Clincial and Patient reported variables will be from Week 0 to

Week 104/Withdrawal Visit and from Week

52 to Week 104/Withdrawal Visit - for details see page 25-27 of the protocol

Study description

Background summary

Rheumatoid arthritis is a chronic systemic inflammatory disease that is associated with significant morbidity and mortality. The disease is characterized by inflammation of the synovial lined diarthrodial joints that can result in pain, swelling and joint damage with secondary deformity and progressive disability and impairment of patient's health related quality of life. It is estimated that about 1% of the population worldwide has RA (Lawrence et al, 1998).

Anti-TNF agents have demonstrated unsurpassed efficacy and have dramatically improved outcomes for patients with RA. Furthermore, the use of biologics has been shown to reduce structural damage of joints evaluated by radiographic assessments, an area where synthetic DMARDS have previously been unsuccessful (Smolen, 2009b). There is extensive evidence to show that the earlier the treatment intervention and the resulting reduction of structural joint damage, the better the long term outcomes (Smolen et al, 2009a; Aletaha et al, 2009)

The treatment of severe, active, and progressive RA in adults not previously treated with MTX or other DMARDs has been included in the indication statement for the anti-TNF, Remicade®, and in adults not previously treated with MTX for the anti-TNFs, Enbrel®, Humira®, and Simponi®. The patient populations enrolled in the supportive clinical studies were MTX*naïve patients with RA disease duration less than 2 or 3 years. It has been reported that joint erosion may occur as early as 6 months from disease onset and that progression of damage can occur rapidly during the first 2 years (Lindqvist et al, 2003). For these reasons, UCB will be evaluating patients early in their disease by requiring patients entered into the study be within 1 year of symptom onset and

diagnosis of RA

Study objective

The study has the following 3 main objectives pertaining to the treatment of DMARD-naïve subjects with adult-onset, early, active, RA, diagnosed within 1 year before Screening using the 2010 ACR/EULAR RA classification criteria:

1.To show that initial treatment with CZP + MTX is more efficacious than initial treatment with PBO + MTX, based on the achievement of sustained remission (defined as DAS28[ESR] <2.6 at Week 40 and Week 52 visits).
2.To demonstrate that LDA (DAS28[ESR] *3.2) can be maintained with continued use of CZP + MTX, using either the standard maintenance dosing or a reduced frequency of CZP administration.
3.To evaluate the safety and efficacy of re-introduction of standard CZP dosing regimen in restoring LDA following a disease flare.

Study design

This is a 24-month (104 week) randomized, double-blind, parallel-group, placebo-controlled Phase 3 study consisting of 2 consecutive periods of 52 weeks each; Period 1 = Week 0 to Week 52 and Period 2 = Week 52 to Week 104. A Safety Follow-Up call will be performed
10 weeks after the last dose of study drug.

Periode 1 ; Subjects will be randomly assigned at Baseline (Week 0) to 1 of 2 treatment groups in a ratio of 3:1

Periode 2 ; Those subjects randomized to the CZP + MTX arm in Period 1 and who are in sustained LDA (defined as DAS28[ESR] *3.2 at Weeks 40 and 52) at Week 52 will be re-randomized to 1 of 3 treatment groups in a ratio of 2:3:2 (standard maintenance dose of CZP 200mg every 2 weeks + MTX, reduced frequency dosing of CZP 200mg every 4 weeks + MTX and PBO + MTX)

Intervention

Subcutaneous injection of Certoluzimab (400 mg once every 2 weeks (period1) or 200 mg once every 4 weeks (period 2)) or placebo together with oral metotrexaat as per SPC for Rheumtoide artheritis.

Study burden and risks

Based on data from clinical studies, more than 12,104 subjects (including at least 463 healthy volunteers, 117 subjects with psoriasis, 4274 subjects with Crohn*s disease and 6,780 subjects with rheumatoid arthritis, 270 subjects with psoriatic arthritis and 200 subjects with axial spondyloarthritis) have

received at least one dose of certolizumab pegol (the study drug). In addition, from data based on post-marketing surveillance (from marketed certolizumab pegol), UCB Pharma SA estimates that more than 30,000 subjects with Crohn's disease or subjects with rheumatoid arthritis have received at least one dose of certolizumab pegol (available on the market since 2008).
Certolizumab pegol has been found to be generally well tolerated and have an acceptable safety profile as a TNF inhibitor in the reported indications.
Side-effects possibly related to certolizumab pegol, reported through post-marketing surveillance, are not different from those reported in the clinical studies.

Subjects undergo a minimal physical examination during each visit. During screening, week 52, week 104 an x-ray of joints and an ECG (heart movie). Bloood sampling will be performed in week 0, 12 and 24, 52, 64, 76,84 and 92 of several analyses.

Tuberculin skin test will be done by placing a needle just under the skin to inject a small amount of fluid. Inserting a needle under the skin causes brief discomfort. Localized pain, bleeding, bruising or infection can occur at the site where injections are given and / or the blood samples are drawn. Some patients may feel dizzy from these procedures. The risk associated with radiation exposure from having an X-ray of chest, hands, wrists and feet is minimal.

The subject has a risk of 1/3 of getting placebo and has chance of side effects including infections and parasitic diseases (15, 5% in patients on Cimzia and 7.6% in patients on placebo) and General disorders and administration site conditions disorders (10% and 9.7% in placebo patients), specifications for text see B1 Cimzia. Also, the safety and tolerability of the Cimzia discussed in detail in the current investigator of Brochure (IB)

Nevertheless, in two Phase 3 studies, CDP870-027 and CDP870-050, CZP 400mg at Weeks 0, 2, and 4 followed by 200mg every 2 weeks was efficacious in reducing signs and symptoms of RA as well as preventing structural damage of the joints.
Certolizumab pegol was also shown to
have rapid onset of action. The RA0055 study will evaluate the initial treatment of DMARD-naïve patients early in their RA disease. Starting treatment with a biological agent combined with a non-biological DMARD has been shown to reduce the progression of structural damage to a larger extent than starting with a non-biological DMARD alone.

Contacts

Public

UCB Pharma

Allée de la Recherche 60
B-1070 Brussels
BE
Scientific
UCB Pharma

Allée de la Recherche 60
B-1070 Brussels
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. An IRB/ IEC approved written Informed Consent form is signed and dated by the subject prior
to any study procedure.
2. To allow collection of blood samples for the genomic, genetic and proteomic analysis the subjects must have signed and dated an IRB/ IEC approved written Pharmacogenomics Informed Consent form.
3. Subject 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.
4. Subject is male or female and must be at least 18 years old at the Screening Visit.
5. 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 method and
spermicide) at Screening. Abstinence only is not an acceptable method. Subjects must agree

to
use adequate contraception during the study and for at least 10 weeks (or longer if required by
local regulations) after the last dose of study treatment. Male subjects must agree to ensure they or their female partner(s) use adequate contraception during the study and for at least 10
weeks (or longer if required by local regulations) after the subject receives their last dose of study treatment.
6. Subjects must have a time since diagnosis of adult-onset RA less than 1 year as defined by the
2010 ACR / EULAR classification criteria from Screening Visit.
7. Subjects must be DMARD-naïve at Screening and Baseline (except antimalarials, see Section
6.2.2).
8. Subjects must have a positive RF or positive ACPA result at Screening.
9. Subjects must have active RA disease as defined by:
* * 4 swollen joints and * 4 tender joints (DAS28 joint) at Screening and Baseline.
* DAS28(ESR) >3.2 at Screening and Baseline.
* CRP *10 mg/L at Screening and/or ESR *28 mm/hour at Screening and Baseline.

Exclusion criteria

1. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 10 weeks following last dose of study drug.
2. The subject has previously participated in this study and has received CZP treatment, or has previously received CZP in or outside of another clinical study.
3. The subject has participated in another study of a medication or a medical device under investigation within the last 3 months or is currently participating in another study of a medication or medical device under investigation.
4. The subject has a known hypersensitivity to any components of CZP or with a history of an adverse reaction to polyethylene glycol (PEG).
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) nor have a Steinbrocker IV functional capacity.
7. Subjects must not have received any experimental nonbiological therapy in the 3 past months or within 5 half-lives prior to Baseline (whichever is longer).
8. Subjects must not have received any experimental or approved biological agent (e.g. anti-TNF therapy, anti-IL1, or IL6, etc) prior to Baseline.
9. Subjects must not have used the following medications in the manner as detailed by the exclusion criteria column in the table 6.1 in the study protocol.
10. Concurrent malignancy or a history of malignancy (subjects with less than 3 excised basal cell carcinomas or with cervical carcinoma in situ successfully surgically treated more

than 5 years prior to Screening may be included).
11. Subjects with a history of a lymphoproliferative disorder including lymphoma or signs and symptoms suggestive of lymphoproliferative disease.
12. Subjects with a history of blood dyscrasias.
13. Subjects with a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease or other significant immunological/inflammatory disease including systemic lupus erythematosus, inflammatory bowel disease.
14. Subjects with congestive heart failure as defined by the New York Heart Association 1994 classification criteria.
15. Subjects with a history of, or suspected, demyelinating disease of the central nervous system (eg multiple sclerosis or optic neuritis).
16. Subjects with any other condition (ie, clinically significant laboratory values) which in the Investigator*s judgment would make the subject unsuitable for inclusion in the study.
17. Subject with a value >1.5x ULN for any of the following liver function tests (LFTs) at Screening:
* Aspartate aminotransferase (AST) (glutamic oxaloacetic transaminase [GOT])
* Alanine aminotransferase (ALT) (glutamate*pyruvate transaminase [GPT])
18. Subject has history of chronic alcohol or drug abuse within the last 1 year.
19. Subject has any medical or psychiatric condition that, in the opinion of the Investigator, can jeopardize or would compromise the subject*s ability to participate in this study.
20. Subjects with history of or current clinically active infection (including infections verified by chest X-ray) with histoplasma, coccidiodes, paracoccidioides, pneumocystis, nontuberculous mycobacteria, blastomyces, or aspergillus.
21. Subjects with a history of chronic or recurrent infections (>3 episodes requiring antibiotics
or antivirals during the preceding year), recent serious or life-threatening infection within the 6 months prior to the Baseline Visit (including herpes zoster), hospitalization for any infection in the last 6 months or any current sign or symptom that may indicate an infection.
22. 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).
23. Subjects with concurrent acute or chronic viral hepatitis B or C.
24. Subjects with known human immunodeficiency virus (HIV) infection.
25. Subjects receiving live or attenuated vaccination within 8 weeks prior to Baseline. Live or attenuated vaccines are not allowed to be used concurrently with CZP during the period of the study.
26. Subjects with known TB disease, high risk of acquiring TB infection, or latent TB infection defined as follows:
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 with a potential close contact with TB infected subjects.
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) (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).
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 *c* is permitted only if treatment for latent TB infection is initiated or has been initiated at least 4 weeks prior to study drug administration and treatment is still ongoing at time of study entry. 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.
- Reports of PPD results not taken at Screening but performed *3 months prior to Screening and reported from elsewhere must be documented with exact induration measurement.

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):	14-08-2012
Enrollment:	50
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	05-03-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Approved WMO

Date:	11-06-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Approved WMO

Date:	17-09-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Approved WMO

Date:	08-03-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-05-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-11-2013
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	EUCTR2011-001729-25-NL
CCMO	NL38097.058.12