A Phase IIIB, multicenter study with a 12-week double-blind, placebo-controlled, randomized period followed by an open-label, extension phase to evaluate the safety and efficacy of certolizumab pegol administered to patients with active rheumatoid arthritis.

Published: 24-12-2008
Last updated: 06-05-2024

Primary Objective:To assess the clinical response rate as measured by American College of Rheumatology 20% (ACR20) response rate at Week 12.Secondary Objective:• To assess:- for all patients at Week 12, and every 8 weeks and at the completion/…

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

Summary

ID

NL-OMON33758

Source
ToetsingOnline

Brief title
C87094 / REALISTIC

Condition

- Other condition

Synonym
reumatoid arthritis, rheumatism

Health condition

reumatoïde artritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: anti-TNF, certolizumab pegol, disease-modifying anti-rheumatic drug (DMARD), rheumatoid arthritis (RA)

Outcome measures

Primary outcome

The primary efficacy variable is the ACR 20% (American College of Rheumatology

20% response criteria) responder rate at Week 12.

Secondary outcome

For all patients at week 12:

- ACR50 and ACR70 responder rate;

- Change from baseline in DAS28(CRP), SDAI and CDAI scores;

- DAS28(CRP) remission (<2.6) rate, SDAI remission (<=3.3) rate and CDAI

remission (<=2.8) rate;

- Change from baseline in individual components of the ACR, including TJC, SJC,

HAQ-DI, CRP, Patient*s assessment of Arthritis Pain-VAS, Patient*s global

assessment of disease activity-VAS and Physician*s global assessment of disease

activity-VAS;

- Time form randomization to sustained ACR20 response at two consecutive visits

or before week 12;

- EULAR response critera.

Every 8 weeks and the completion/withdrawal visit in the group remaining in the study after week 12:

- ACR20/50/70 responder rate.

- Change from baseline in DAS28(CRP), SDAI and CDAI scores.

- DAS28(CRP) remission (<2.6) rate, SDAI remission (<=3.3) rate and CDAI remission (<=2.8) rate

- Change from baseline in individual components of the ACR, including TJC, SJC, HAQ-DI, CRP, Patient*s assessment of Arthritis Pain-VAS, Patient*s global assessment of disease activity-VAS and Physician*s global assessment of disease activity-VAS.

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 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.

RA is a difficult disease to manage: the disease course is often unpredictable and currently available therapies are associated with varying degrees of efficacy and can be associated with significant toxicity. Treatment for RA includes use of non-steroidal anti-inflammatory drugs (NSAIDs), cyclooygenase-2 (COX-2) selective inhibitors, corticosteroids and disease-modifying antirheumatic drugs (DMARDs).

Given the accumulating data indicating that there is a benefit in using more aggressive (i.e. DMARD) therapy earlier in the disease course (as well as the combination of DMARD therapy), there has been a need for more efficacious and/or better-tolerated therapies. A significant addition to the therapeutic armamentarium of RA has been the development of a new category of DMARDs referred to as the biologic response modifiers, particularly tumor necrosis factor alpha (TNFα) neutralizing therapies.

The pro-inflammatory cytokine Tumor Necrosis Factor α (TNFα) has been shown to have a central role in RA.

Certolizumab pegol (CZP) is an engineered, humanized, antibody Fab* fragment produced in E. coli with specificity for human TNFα that is conjugated to polyethylene glycol (PEG).

Combination therapy with traditional DMARDs plus anti-TNF agents in patient with an incomplete response to DMARDS has shown to be significantly better in reduction of disease activity, improvement of physical function, retardation of radiographic progression and induction of clinical remission compared to DMARD-monotherapy. Thus, anti-TNF therapy is an important advance in the therapy of RA.

Certolizumab pegol (CZP) is effective in the treatment of rheumatoid arthritis (RA), when combines with methotrexate (MTX) or given as monotherapy. However, a detailed assessment of CZP in combination with a wide range of traditional DMARDs commonly used to treat patients with RA in clinical practice is lacking.

There is insufficient data with CZP in patients previously treated with anti-TNF agent(s). There is a need for additional data to document the safety and efficacy of switching among TNF antagonists in clinical practice, in order to guide the choice of treatment after failure of an anti-TNF therapy.

Study objective

Primary Objective:
To assess the clinical response rate as measured by American College of Rheumatology 20% (ACR20) response rate at Week 12.

Secondary Objective:
• To assess:
- for all patients at Week 12, and every 8 weeks and at the completion/withdrawal visit in the group remaining in the study after Week 12:
- clinical response rate.
- reduction of disease activity.
- achievement of clinical remission.
- additionally, at Week 12:
- improvement in individual components of the ACR criteria

- Time to sustained ACR20 response.
- European League Against Rheumatism (EULAR) response.
- additionally, every 8 weeks and at completion/withdrawal visit :
- change from Baseline in individual components of the ACR criteria.

• Tolerability and safety of CZP therapy over the first 12 weeks of treatment and over the open-label treatment extension period.

• To evaluate the influence of some characteristics (as per protocol) on ACR20 response rate at Week 12 and adverse events rate with CZP therapy.

Study design

A Phase IIIb, multicenter study with a 12-week double-blind placebo-controlled randomized period, followed by an open-label extension phase.

Intervention

Patients will receive CZP 400 mg at week 0, 2, and 4 followed by 200 mg every two weeks or placebo up to and including week 10.
From week 12 all patients will receive treatment with open-label CZP 200 mg very other week.

During the double-blinded phase the study drug will be administered at the hospital by appropriate study personnel. Patients of the open-label phase patients will be trained at the hospital to self administer. Patients who are able to self administer CZP and having the appropriate storage conditions at their homes will be given the opportunity to have home based self administration.

Study burden and risks

The burden exists of the sc injections with study medications for which the patient has to visit the hospital every other week during the first 12 weeks. After 12 weeks the patient will be offered to perform self-injection. In this case, the hospital has only to be visited every 8 weeks.

Benefits:
CZP 400 mg sc every week was efficacious in reducing signs and symptoms of RA as well as preventing structural damage of the joints. CZP was also shown to have rapid onset of action in two phase 3 studies.
The benefits of the C87094 protocol are the potential future availability of a new treatment for RA, with potential efficacy demonstrated across a broader population of RA patients.

Risks:

CZP is as TNFα antagonist known to be associated with infections requiring treatment and reactivation of latent tuberculosis. An association has also been reported with development of leukemia and lymphoma (not known whether causal relationship or confounder factors). Other adverse events that have been infrequently reported in patient treated with TNFα antagonist include congestive heart failure, drug-induced lupus, seizures, demyelinating disorders and pancytopenia.

There is currently insufficient safety data to determine whether CZP treatment is also associated with these AEs. The C87094 protocol excludes patients thought to be at increased risks of such AEs.

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. Patients must have a diagnosis of adult-onset RA of at least three months duration as defined by the 1987 American College of Rheumatology classification criteria.
2. Patients must have active RA disease as defined by:
• >=5 tender joints (28 joint count) at Screening and Baseline; and
• >=4 swollen joints (28 joint count) at Screening and Baseline; and
• >=10 mg/L CRP and/or >=28mm/hour ESR (Westergren) at screening.
3. Patients must have had an unsatisfactory response or intolerance to at least one traditional DMARD.

Exclusion criteria

1. Patients must not have a diagnosis of any other inflammatory arthritis (e.g., psoriatic arthritis or ankylosing spondylitis).
2. Patients must not have >3 arthroplasties due to RA and/or Steinbrocker IV functional capacity.
3. Patients must not have a secondary, non-inflammatory type of arthritis (e.g. osteoarthritis or fibromyalgia) that in the Investigator*s opinion is symptomatic enough to interfere with evaluation of the effect of study drug on the patient*s primary diagnosis of RA.
4. Patients must not have a history of an infected joint prosthesis at any time with that prosthesis still in situ.
5. Patients must not have received any biological therapy for RA within two months prior to Baseline visit, except for etanercept or anakinra for which a one month washout prior to baseline visit is acceptable.
6. Patients having discontinued or discontinuing biological therapy for their RA must not have had a severe hypersensitivity reaction or an anaphylactic reaction to more than 1 different biologic agent.
7. Patients must not have received treatment with more than 2 anti-TNF agents prior to enrollment in this trial.
8. Patients must not have received treatment with rituximab and/or abatacept.
9. Patients 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.
10. Patients with active TB (or history of active TB), positive chest X-ray for TB, or positive PPD skin test or patients having close contact with an individual with active TB. Patients having a PPD skin test >= 5 mm can enter the study, provided that active TB is excluded and provided that they are adequately treated for latent TB and provided that treatment is initiated at least 1 month prior to first administration of CZP.
11. Patients at a high risk of infection (e.g. leg ulcers, indwelling urinary catheter and persistent or recurrent chest infections and patients who are permanently bedridden or wheelchair bound).
12. Patients with a history of a lymphoproliferative disorder including lymphoma or signs and

symptoms suggestive of lymphoproliferative disease.
13. Patients with known concurrent acute or chronic viral hepatitis B or C.
14. Patients with known human immunodeficiency virus (HIV) infection.
15. Patients receiving any vaccination (live or attenuated) within eight weeks prior to baseline (e.g., parenteral influenza and pneumococcal vaccines are allowed, but nasal influenza vaccine is not).
16. Concurrent malignancy or a history of malignancy (other than carcinoma of the cervix or basal cell carcinoma successfully treated more than five years prior to screening).
17. Patients with a current or recent history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological or cerebral disease.
18. Patients with class III or IV congestive heart failure according to the New York Heart Association (NYHA) 1964 classification criteria.
19. Patients with a history of, or suspected, demyelinating disease of the central nervous system (e.g. multiple sclerosis or optic neuritis).
20. Patients with a history of an adverse reaction to PEG.
21. Patients must not have a change in dose regiment for NSAIDs/COX-2 inhibitors 7 days prior to baseline, nor a change in dose regiment for oral corticosteroids 14 days prior to baseline. Patients must also not have received IM/IV/IA corticosteroids nor IA hyaluronic acid within 28 days prior to baseline. Patients must also not have received DMARDs within 3 months prior to baseline.

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):	03-08-2009
Enrollment:	60

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Certolizumab pegol (Cimzia®)
Generic name:	-

Ethics review

Approved WMO Date:	24-12-2008
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-04-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-06-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-01-2010
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	EUCTR2008-005427-28-NL
ClinicalTrials.gov	NCT00717236
CCMO	NL25860.058.08