PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE EFFICACY AND SAFETY OF CERTOLIZUMAB PEGOL IN SUBJECTS WITH ACTIVE AXIAL SPONDYLOARTHRITIS (AXIAL SPA)

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Certolizumab pegol is a PEGylated humanized Fab* fragment with specificity for humanTNF*. Certolizumab pegol has demonstrated efficacy in clinical studies of Crohn*s disease(CD), psoriasis (PSO), and RA. The objective of this study is to demonstrate...

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

Summary

ID

NL-OMON36612

Source
ToetsingOnline

Brief title
AS001

Condition

- Joint disorders

Synonym
Ankylosing Spondyloarthritis, Bechterew's Disease

Research involving

Human

Sponsors and support

Primary sponsor: UCB BIOSCIENCES GmbH
Source(s) of monetary or material Support: SCHWARZ BIOSCIENCES;GmbH (UCB Group)

Intervention

Keyword: Adult -Onset, Axial Spondyloarthritis, Double-blind, Phase 3

Outcome measures

Primary outcome

The primary objective of the study is to demonstrate the efficacy of CZP

administered sc at

the doses of CZP 200mg Q2W and CZP400mg Q4W after a loading dose of CZP 400mg at

Weeks 0, 2, and 4 on the signs and symptoms of active axial SpA.

Secondary outcome

The secondary objectives of the study are to assess the effects on safety and

tolerability and

to demonstrate the effects of CZP on:

- Health outcomes

- Partial remission

- Spinal mobility

- Structural damage and inflammation in the subpopulation of subjects with MRI

Study description

Background summary

Axial spondyloarthropathy comprises a spectrum of early to late stage diseases,

the most well
acknowledged of these being ankylosing spondylitis (AS) and the earliest or least well
defined being preradiographic axial SpA. Axial SpA usually starts with sacroiliitis which is
not detectable by conventional radiography. During the early disease stage, MRI may detect
acute inflammatory lesions in the absence of radiographic sacroiliitis. With time, sacroiliitis
and possibly syndesmophytes may become detectable by conventional radiography. Back
pain, often the initial symptom, may be present throughout the disease course.
Most characteristic and pathognomonic for AS is the growth of syndesmophytes and other
features of new bone formation, possibly leading to ankylosis and spinal fusion. Conventional
radiography, the *gold standard* in imaging of AS for the past decades, has been included in
the internationally accepted ASAS core set for AS. However, the presence of radiographic
changes should be seen as a marker of disease chronicity and possibly severity, rather than as
an essential diagnostic criterion. Data support the fact that the occurrence of radiographic
sacroiliitis in subjects with axial SpA is mainly a function of time, with some influence from
disease severity. The absence and presence of radiographic sacroiliitis in subjects with SpA
represent early to later stages of a single disease continuum and, therefore, the same disease
entity.
Ankylosing spondylitis, the most defined subset of the axial SpAs, is a chronic inflammatory
rheumatic disease that affects about twice as many young men than women in the second and
third decade of life with a prevalence of 0.2 to 1.2% worldwide. Like the other axial SpAs,
the main clinical symptom is inflammatory back pain. In most patients the disease starts in
the sacroiliac joints and spreads to the spine. Extra-articular features may include
involvement of the bowel (colitis), the eye (uveitis), and the skin (psoriasis). Disability
increases with increasing duration of disease; 30% of the subjects have severe disease often
accompanied by considerable functional loss.
Conventional treatment of AS has included NSAIDs and physiotherapy. The key

aims of
treatment in AS have included control of pain and stiffness, as well as
reducing damage,
disability, and loss of function. However, disease-modifying antirheumatic
drugs (DMARDs)
and corticosteroids, although having significant efficacy to reduce damage,
disability, and
loss of function in rheumatoid arthritis (RA), have had limited or no similar
benefit in
subjects with AS. Use of DMARDs such as sulfasalazine (SSZ) and methotrexate
(MTX) has
been primarily for controlling symptoms in subgroups of AS subjects with
peripheral arthritis
and remitting anterior uveitis. As a result, in the past, a delayed diagnosis
of AS or axial SpA
did not have much of an adverse consequence since the available therapies were
not highly
effective.
Most recently, treatment with TNF*-antagonists has demonstrated marked
improvement of
almost all features of AS, such as clinical disease activity, physical
function, spinal mobility,
peripheral arthritis, and enthesitis. Four TNF*-antagonists are currently
registered in the
United States of America (USA) and/or Europe (infliximab [IFX], etanercept
[ETN], and
adalimumab [ADA] in both the USA and Europe and golimumab [GOL] in the USA) for
the
treatment of AS. Recent data also show that AS subjects with a short disease
duration and
good functional status are more likely to respond to TNF-antagonists than
subjects with long-standing disease and impaired function (Pradeep et al, 2008;
Sieper and Rudwaleit, 2005; Rudwaleit et al, 2008). Thus, an early and reliable
diagnosis of AS and axial SpA has
now become an important and very relevant issue. Based on similarities in AS
and axial SpA, it would be expected that TNF blockade might
also have a benefit in the treatment of axial SpA. Indeed, early studies in
subjects with axial
SpA have shown the TNF-antagonists ADA and IFX to be efficacious (Haibel et al,
2008;
Barkham et al, 2009).

Study objective

Certolizumab pegol is a PEGylated humanized Fab* fragment with specificity for
human
TNF*. Certolizumab pegol has demonstrated efficacy in clinical studies of

Crohn*s disease
(CD), psoriasis (PSO), and RA. The objective of this study is to demonstrate the effects of
CZP in the treatment of axial SpA. Two dose regimens of CZP have been selected for this
study, reflecting 2 different frequencies of administration: 3 loading doses of CZP 400mg
administered sc at Weeks 0, 2, and 4 followed by either CZP 200mg Q2W or CZP 400mg
Q4W.
The proposed CZP dosing regimens for this study were selected on the basis that these doses
of CZP have been efficacious for the treatment of RA in clinical studies, are the
recommended dosing regimens in RA, and would be expected to have similar efficacy in
axial SpA. Furthermore, ADA, ETN, and GOL, the 3 commercially available sc
TNF-antagonists for the treatment of AS, have identical recommended dosing regimens in
AS and RA and also have similar efficacy and safety profiles in both indications.
The classical modified New York (NY) diagnostic criteria for AS requires the presence of
definite sacroiliitis of either grade 2 bilaterally or grade 3 or 4 unilaterally on radiographs. As
subjects with early AS may not have radiographic sacroiliitis, it has been proposed to classify
subjects with inflammatory back pain from predominantly axial involvement as axial SpA
regardless of whether they have definite radiographic sacroiliitis. The new ASAS
classification criteria include, besides the presence of chronic back pain for more than
3 months with an onset before 45 years of age, either the presence of sacroiliitis by
radiographs or by MRI plus at least one clinical parameter (*imaging definition*) or the
presence of human leucocyte antigen B27 (HLA-B27) plus at least 2 clinical parameters
(*clinical definition*). In the present protocol, it is proposed to study the efficacy of CZP, a
TNF-antagonist, in subjects who meet the diagnosis of axial SpA by the new imaging
definition of the ASAS criteria which would include those subjects meeting the classical
modified NY classification criteria (Rudwaleit et al, 2009a; Rudwaleit et al, 2009b).

Study design

Study AS001 is a multicenter, randomized, double-blind, parallel-group, placebo-controlled
clinical study to evaluate the efficacy and safety of CZP in adult subjects with active axial SpA.

The study includes 5 periods:

Period 1
Screening period of 1 to 5 weeks in order to obtain laboratory data, to verify that the doses of MTX, NSAIDs, and corticosteroids, if used, are stable, and to enable washout of any medications not permitted for use during the study.

Period 2 * Week 0 to Week 24: Double-blind, placebo-controlled
Eligible subjects will be allocated to the following study treatments in a 1:1:1 ratio:
- CZP administered sc at the dose of CZP 400mg Q2W at Weeks 0, 2 and 4 followed by CZP 200mg Q2W sc (starting at Week 6)
- CZP administered sc at the dose of CZP 400mg Q2W at Weeks 0, 2 and 4 followed by CZP 400mg Q4W sc (starting at Week 8)
- Placebo

Study treatments (including placebo) will be administered by dedicated unblinded trained site personnel at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.
After the Week 24 Visit of the last subject, the database will be locked and a first interim study report will be written. Limited UCB personnel will become unblinded for the purposes of the data analysis but the Investigator and the subject will remain blind to treatment assignments. All subjects will switch to active treatment after Week 24.

Period 3 * Week 24 to Week 48: Dose-blind for the subjects and the Investigators, no placebo
Subjects originally randomized to placebo will be re-randomized in a 1:1 ratio to receive 3 loading doses of CZP sc 400mg at Weeks 24, 26, and 28 followed by either CZP 200mg Q2W or CZP 400mg Q4W from Week 30 onward.
All subjects originally randomized to CZP will continue to receive the treatment regimen they were assigned to at randomization (CZP 200mg Q2W or CZP 400mg Q4W sc).
Study treatments will be administered by dedicated unblinded trained site personnel according to the injection scheme. All subjects will be trained on self-administration at Weeks 26 and 28. Subjects will self-administer 1 injection at home Q4W starting from Week 30.
After the Week 48 Visit of the last subject, the database will be locked and a second interim study report will be written.

Period 4 * Week 48 to Week 158: Open-label
Subjects will continue to receive the same dose regimen of CZP that they received during Period 3. After Week 48, only subjects randomized to CZP 200mg Q2W will self-administer CZP 200mg (one-1mL sc injection) Q4W at home. All other injections will be administered preferably by self-administration during scheduled visits.
The last dosing visit will be at Week 156. The final study assessments are performed at Week 158.

Period 5 * Week 158 to Week 166: Safety Follow-Up
All subjects, including those withdrawn from study treatment, will have a Safety Follow-Up Visit 10 weeks after their last dose of study medication.

Intervention

Subjects will receive treatment with Certolizumab by injections of 1 ml syringes.

Study burden and risks

For each subject the study will last up to the maximum of 171 weeks, consisting of the following periods:

- A screening period that lasts up to 5 weeks
- A double blind placebo controlled treatment period of 24 weeks
- A dose blind treatment period of 24 weeks
- An open label treatment period of 110 weeks
- A safety follow up visit 10 weeks after the last dose of study medication.

During these visits the subjects will undergo:

- Physical Examination
- Vital signs/function tests
- Questionnaires about general condition, disease and related problems
- Tuberculosis test
- pregnancy test
- Vena punction (max 25 ml per visit)
- Subcutaneous injection (max 1 ml per visit)
- X-ray of chest, hands and feet

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

To be eligible to participate in this study, all of the following criteria must be met:
1. Subject must be at least 18 years old at the Screening Visit.
2. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent is signed and dated by the subject.
3. The subject is considered reliable, willing and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the Investigator.
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 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.
5. Subjects must have a documented diagnosis of adult-onset axial SpA of at least 3 months* duration as defined by the ASAS criteria with sacroiliitis documented by x-ray or MRI.

6. Subjects must have active disease as defined by
- BASDAI score * 4
- Back pain * 4 on a 0 to 10 NRS (from BASDAI item 2)
7. Subjects must have been intolerant to or had an inadequate response to at least 1 NSAID. Inadequate response to an NSAID is defined as lack of response to at least 30 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID or the lack of response to treatment with at least 2 NSAIDs at the maximum tolerated dose for 2 weeks each.

Exclusion criteria

1. The subject has previously participated in this study or has previously received CZP treatment in or outside of another clinical study.
2. 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.
3. Subject has history of chronic alcohol abuse (more than 14 drinks/units per week for women and 21 drinks/units for men [1 drink=4oz of wine, 12oz of beer, or 1oz of hard liquor] or 330mL of 5% alcohol by volume beer=2 units, 125mL of 12% wine=1.5 units, 50mL of 40% spirits=2 units) or drug abuse within the last year.
4. Subject has any medical or psychiatric condition (according to the Diagnostic and Statistical Manual of Mental Disorders [DSM] criteria) that, in the opinion of the Investigator, can jeopardize or would compromise the subject*s ability to participate in this study.
5. Subject has a known hypersensitivity to any components of CZP, placebo or with a history of an adverse reaction to polyethylene glycol (PEG).
6. Subjects must not have a diagnosis of any other inflammatory arthritis (eg, RA, systemic lupus erythematosus, sarcoidosis).
7. Subjects must not have total spinal ankylosis (*bamboo spine*) or a secondary, noninflammatory condition (eg, osteoarthritis or fibromyalgia).
8. Subjects must not have used the following medications in the manner as detailed by the exclusion criteria in the table in the protocol amendment 1 on page 36.
9. Known TB disease, high risk of acquiring TB infection, or latent TB infection;For the rest of the exclusion criteria, please refer to Protocol Amendment 1 23 Nov 2009 page 34.

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):	08-09-2010
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cimzia
Generic name:	CERTOLIZUMAB PEGOL
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	23-03-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	29-06-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	30-06-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	02-11-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-03-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-03-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-06-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-06-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-02-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-03-2013
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	EUCTR2009-011719-19-NL
CCMO	NL31144.068.10
Other	registratie is nog bezig. Nog niet voltooid