A MULTICENTER OPEN LABEL STUDY OF ETANERCEPT WITHDRAWAL AND RETREATMENT IN SUBJECTS WITH NON RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS WHO ACHIEVED ADEQUATE 24 WEEK RESPONSE

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Primary Objective* To estimate the proportion of subjects who flare within 40 weeks followingwithdrawal of ETN in subjects who have achieved ASDAS CRP less than1.3 (inactive disease).Secondary Objectives* To estimate time to flare after withdrawal...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON42652

Source
ToetsingOnline

Brief title
A MULTICENTER OPEN LABEL STUDY OF ETANERCEPT

Condition

- Other condition
- Autoimmune disorders
- Connective tissue disorders (excl congenital)

Synonym
AXIAL SPONDYLOARTHRITIS

Health condition

AXIALE SPONDYLOARTRITIS

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer Inc
Source(s) of monetary or material Support: Industry (Pfizer)

Intervention

Keyword: Axial Spondyloartritis, Etanercept, Retreatment, Withdrawal

Outcome measures

Primary outcome

The primary endpoint is the occurrence of flare (defined as an ASDAS ESR

greater than or equal to 2.1) within 40 weeks following withdrawal of ETN.

Secondary outcome

The following key secondary endpoint will be estimated:

• The time to flare following withdrawal of ETN (as measured from treatment

withdrawal until ASDAS ESR greater than or equal to 2.1).

The following secondary endpoints and outcome measures will be estimated within

40 weeks following withdrawal of ETN and during the 12 week re-treatment period

(if applicable):

• Occurrence of ASDAS CRP less than 1.3 (inactive disease);

• Occurrence of ASAS 20 and ASAS 40;

• Occurrence of ASAS partial remission;

• ASDAS;

• Occurrence of ASDAS major improvement and clinically important improvement;

• Nocturnal and total back pain;

• Bath Ankylosing Spondylitis Functional Index (BASFI) and its components;

• Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and its components;

• Occurrence of BASDAI 50;

• High sensitivity C Reactive Protein (hsCRP);

• Health Outcomes Assessments using the following instruments: EuroQoL-5D Health Questionnaire (EQ-5D), SF-36 and Work Productivity and Activity Impairment (WPAI);

• MRI SIJ/spine as measured by Spondyloarthritis Research Consortium of Canada (SPARCC).

The following secondary endpoint will be estimated over 12 weeks following re-treatment of subjects who flare:

• Time to ASDAS inactive disease after re-treatment. Other endpoints:

• Subject Assessment of Disease Activity (SADA);

• Physician Global Assessment (PGA);

• Bath Ankylosing Spondylitis Patient Global Assessment Score (BAS-G);

• Tender and swollen joint counts (44 count);

• Dactylitis and enthesitis score (Maastricht Anklyosing Spondylitis Enthesitis Score [MASES]

Safety Endpoints:

Safety will be assessed throughout the study. The following variables will be assessed: physical examination, vital signs, hematology, chemistry, urinalysis, premature withdrawal, inflammatory bowel disease (IBD), psoriasis, and uveitis

evaluations, adverse events and serious adverse events during the study.

Study description

Background summary

Axial Spondyloarthritis (ax SpA) is a chronic disease whose most devastating clinical manifestation is the loss of mobility. Commonly ax SpA progresses from sacral inflammation to progressive spine ankylosis over time. Since patients with early disease may not show x-ray abnormalities related to SpA, new technologies such as MRI are increasingly being utilized. The Assessment of SpondyloArthritis international Society (ASAS) recently created a classification system for ax SpA based on whether patients meet clinical criteria or imaging criteria. Patients meeting the ASAS criteria for ax SpA without evidence of sacroiliitis on x-ray are classified as having nr-ax SpA. With the advent of new consensus based criteria that allow earlier identification of patients with ax SpA, before significant x-ray abnormalities develop, earlier therapeutic intervention may potentially impact the natural history of the disease by shutting down early inflammation, as this may be the forerunner of irreversible bony ankylosis. In several recent studies, anti-tumor necrosis factor (TNF) agents, including ETN, demonstrated efficacy in patients with nr-ax SpA.
However, additional long-term data are needed, and little is known about the effects of ETN withdrawal in subjects who have achieved a significant clinical response.

In a small trial (ESTHER) of etanercept-treated patients who had achieved an ASAS partial remission after 48 weeks of etanercept treatment, 13 with nr-ax SpAwere withdrawn from therapy. The flare rate in year 2 was 69%, and the mean time to flare was 24.4 weeks .
Retreatment with etanercept showed an improvement in all clinical (BASDAI, ASDAS, CRP) and imaging (MRI SIJ, MRI spine, MRI enthesitis) variables. Only a portion of the subjects re-established remission status (56% ASAS remission; 44% MRI remission; 33% MRI plus ASAS remission).
In study B1801031, patients with nr-ax SpA given a 12 week course of ETN had significantly reduced clinical signs and symptoms as well as sacroiliac joint (SIJ) and spinal inflammation on MRI as compared to patients receiving placebo. An open-label extension is currently underway to examine long-term efficacy and safety.
Little is known about the effects of ETN withdrawal in subjects who have achieved a significant clinical response. A small study with a mixture of AS and nr-ax SpA patients having achieved a significant clinical response showed that approximately 75-80% of subjects had relapses after 2 years. After retreatment, only about a third recovered the level of clinical response they

had achieved at the time of withdrawal. However, firm conclusions regarding the effects of withdrawal and retreatment could not be drawn due to the low numbers of patients in the study. The proposed study is a follow up of this small pilot study that will further our understanding of the benefits and risks of ETN withdrawal in patients who have achieved a significant clinical response. Much is known already from B1801031 about relapse rates of those achieving remission and continuing on ETN, therefore an open-label study estimating the relapse rates in such patients withdrawn from ETN is planned.

Study objective

Primary Objective
* To estimate the proportion of subjects who flare within 40 weeks following withdrawal of ETN in subjects who have achieved ASDAS CRP less than 1.3 (inactive disease).

Secondary Objectives
* To estimate time to flare after withdrawal of ETN, and to compare it to that in
patients from B1801031 who continued ETN therapy.
* To estimate the efficacy of 12 weeks of retreatment in subjects who experience a flare
after withdrawal of ETN.
* To estimate the efficacy of ETN over 24 weeks of initial treatment.
* To estimate the safety and tolerability of ETN in this population.

Study design

This multicenter, open-label, three period study will evaluate withdrawal and retreatment of ETN in subjects with nr-ax SpA who achieved an adequate response, as measured by ASDAS CRP less than 1.3 (inactive disease) following 24 weeks of treatment. The study is expected to randomize approximately 200 subjects in Period 1, in order to have approximately 96 subjects qualify for Period 2.
Period 1:
This is an open-label, 24-week period in which all eligible subjects with nr-ax SpA will be enrolled and treated with ETN 50 mg once weekly plus a stable background NSAID at the optimal tolerated anti-inflammatory dosage as determined by the investigator. The target for this period is therapeutic response defined as achieving Ankylosing Spondylitis Disease Activity Scale C-reactive protein (ASDAS CRP) less than 1.3 at Week 24. Subjects who qualify at Week 24 will enter Period 2 after all Period 1 procedures are completed. Subjects who do not achieve ASDAS CRP less than 1.3 will not enter Period 2 and will complete the study following the Week 28 day follow-up phone call/visit.
Period 2:
The Week 24 visit ends Period 1 and marks the beginning of Period 2. This is a

40-week withdrawal period where subjects will discontinue ETN following the Week 24 dose, yet maintain the background NSAID. If the subject has not flared by the Week 64 visit, their participation in the study is complete.
Period 3:
Subjects who flare (defined as an ASDAS ESR greater than or equal to 2.1) during Period 2 will enter a retreatment period and receive approximately 12 weekly doses of open-label ETN. Subjects experiencing increased disease activity can come into the office any time for an evaluation; if flare criteria are met, open-label ETN is started at this unscheduled visit. If the subject has experienced increased disease activity during Period 2, but does not meet the
protocol defined criteria for flare, it is the investigator*s judgment to determine if the subject should remain in the study or discontinue the study to pursue alternative treatment.
Follow-up ;
A safety follow-up phone call/visit will only be completed for subjects who:
* Receive investigational product (IP) in Period 1, but who do not enter Period 2, or,
* Enter Period 2 and discontinue from the study before the Week 28 visit or,
* Enter Period 3 (Retreatment period).
The purpose of this visit is to assess any new and/or ongoing adverse events and will be performed approximately 28 days after the last dose of IP. This follow-up visit will be done by telephone, unless local regulations require a visit to the study site.

A safety follow-up visit does not need to be completed for subjects who discontinue from the
study after the Week 28 visit and who do not enter Period 3 for retreatment.

Intervention

Among others: treatment with ETN and stop current treatment (if applicable), participating in a Clinical Trial with a number of tests, blood samplings, questionnaires, visits to the hospital.

Study burden and risks

ETN is an approved medicine in NL (Enbrel). Overall, the benefits of ETN administration in patients with nr-ax SpA are expected to include reduced disease activity, including less pain, reduced inflammation of the SIJ, and improved physical function. Based on the safety experience from the B1801031 study
combined with the long-term safety data and post-marketing safety experience in AS, an acceptable safety profile is expected in nr-ax SpA patients treated with ETN. Consequently, the risk-benefit balance of ETN for the treatment of nr-ax SpA is considered to be positive in patients who have high disease activity

despite treatment with NSAIDs. Furthermore, the risk benefit may be more favorable in patients with objective evidence of inflammation,
ie, those who have high CRP and/or MRI inflammation. The proposed study will further our understanding of the benefits and risks of ETN withdrawal in patients who have achieved a significant clinical response. In addition, please refer to appendix 3 of the Informed Consent form.

Contacts

Public
Pfizer Inc

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New York 10017
US
Scientific
Pfizer Inc

East 42nd Street 235
New York 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Period 1:
1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
2. Subjects who are willing and able to comply with scheduled visits, treatment plan,

laboratory tests, and other study procedures.
3. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the entire study and
for 28 days after the last study visit:
• Have undergone a documented hysterectomy and/or bilateral oophorectomy;
• Have medically confirmed ovarian failure; or Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.
4. Duration of symptoms of >=3 months and <5 years at the time of consent.
5. Diagnosis of ax SpA as defined by the ASAS criteria.
The ASAS criteria state that subjects have to have >=3 months of back pain and age of onset <45 years, and:
• Sacroiliitis on imaging plus 1 SpA feature
OR
• Positive Human Leucocyte Antigen B27 (HLA-B27) plus 2 SpA features.
Sacroiliitis on imaging is defined as either:
• Active inflammation on MRI highly suggestive of sacroiliitis associated with SpA
OR
• Defined radiographic sacroiliitis according to the Modified NY criteria.**
**Subjects in this study cannot meet the criteria based on the second bullet (since defined radiographic sacroiliitis is an exclusion criterion).
In order to meet the imaging criteria for ASAS, subjects must have positive sacroiliitis on MRI based on readings performed by the central imaging vendor. This criterion cannot be based on local MRI evaluation or historical MRIs.
If a subject has negative sacroiliitis on MRI, then they must have positive HLA-B27 plus 2 SpA features. Conversely, if a subject is HLAB27 negative, then they must have positive sacroiliitis on MRI and at
least 1 SpA feature.
The SpA features are listed below;
• Inflammatory back pain;
• Arthritis;
• Enthesitis (heel);
• Uveitis;
• Dactylitis;
• Psoriasis;
• Crohn's/ Colitis;
• Good response to NSAIDs;
• Family history of SpA;
• HLA-B27;
• Elevated hsCRP.
6. Subjects must have positive MRI findings (active inflammation on MRI highly suggestive of sacroiliitis associated with SpA) and/or positive hsCRP (defined as hsCRP >3 mg/l).
7. Active symptoms defined by an ASDAS CRP greater than or equal to 2.1 at the screening visit.
8. Back pain with a less than favorable response to current intake of an NSAID at the optimal

tolerated dose as determined by the investigator.
Subjects must have experienced less than favorable response to at least 2 NSAIDs (including the current one) taken separately at the optimal tolerated dose with a total combined duration of >4 weeks.
9. Subject must be taking a stable dose of an NSAID for at least 14 days before the first dose.
10. Female or male 18 years or older (20 or older if required by local regulations) but less than 50 at the time of consent.
11. In the opinion of the investigator, subject is reasonable candidate for treatment with ETN.
12. No contraindication to MRI examination (metal implants or inability to lie flat for 30-60 minutes for example).
13. Negative serum pregnancy test performed at screening, negative urine pregnancy test performed prior to the first dose and negative serum pregnancy test collected for analysis prior to the first dose.
14. Ability to self-inject investigational product or have a designee who can do so.
15. Ability to store injectable investigational product under refrigerated conditions.
16. Demonstrated an adequate screening for tuberculosis (TB) in accordance with local country guidelines.
17. Subject is able to complete health outcomes assessments and investigational product diary.
Period 2:
1. Completion of Period 1.
2. Subjects must achieve ASDAS CRP (inactive disease) less than 1.3 at the Week 24 visit in order to be eligible to enter Period 2.
Period 3:
Subjects must meet the criteria for flare in order to be eligible to enter Period 3. Flare is defined as ASDAS ESR greater than or equal to 2.1.

Exclusion criteria

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.
2. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks before the current study begins and/or during study participation. Participation in studies involving investigational drug greater than 4 weeks to one year before the current study begins will be permitted on a case-by-case basis.
3. Radiological sacroiliitis Grades 3-4 unilaterally or Grade >=2 bilaterally as defined by the NY criteria. Only results from the central imaging reader will determine eligibility. In all countries except Germany:
Historical x-rays (obtained within 4 months of screening) may be utilized, however these subjects
must exhibit radiological sacroiliitis Grade 0-1 unilaterally or Grade 0 bilaterally.
4. Any previous treatment with a tumor necrosis factor-alpha (TNF-*) inhibitor, B/T cell inhibitor or other biologic or immunosuppressive agent for a condition other than IBD.
5. Subject is currently being treated or had previous treatment within 6 months for IBD with

any tumor necrosis factor-alpha (TNF-*) inhibitor or any other immunosuppressant.
6. Evidence of IBD flare within 6 months of first dose.
7. Evidence of active uveitis within 6 months of first dose.
8. Any current or past orthopedic or medical condition that in the opinion of the investigator could cause chronic back pain.
9. Subject has known or suspected allergy, hypersensitivity, or contraindication to ETN, its excipients, or other compounds, related to this class of medication.
10. Subject has concurrent treatment with more than 1 NSAID within 14 days at first dose. Aspirin use, at daily doses up to 325 mg if indicated for cardiovascular protection is permissible and will not be counted as an additional NSAID.
11. Disease modifying anti-rheumatic drugs (DMARDs) other than methotrexate (MTX), sulfasalazine and hydroxychloroquine taken within 4 weeks of first dose. Subjects may be taking only one allowable DMARD at a time.
12. Subject has had an oral dose of prednisone >10 mg/day (or equivalent) or has had a dose change within 4 weeks of first dose.
13. Subject has received an intra-articular, intravenous, intramuscular, or subcutaneous (SC) corticosteroid within 4 weeks of first dose.
14. Subject has current or recent (within 2 years of screening) active TB infection.
• Subjects with remote history (more than 2 years before screening) of active TB are allowed if clear documentation of completion of adequate treatment (as defined by local guidelines) exists.
• Local country guidelines should be observed for appropriate TB screening in the setting of anti-TNF therapy, including a minimum of a chest radiograph and objective TB testing such as a purified protein derivative (PPD) or Quantiferon depending on what is acceptable per local guidelines.
15. Subject has untreated latent TB. (Subjects with known latent TB may be allowed only if local guidelines are followed for therapy and if treatment for latent TB has been adequately completed or initiated at least 4 weeks prior to screening.)
16. Subject has received treatment for latent TB during screening and has had alanine aminotranferase (ALT) and/or aspartate aminotranferase (AST) >=2 times the upper limit of normal (ULN) during this period.
• For subjects that have been diagnosed with latent TB and started treatment during the screening period, additional blood samples for ALT and AST must be drawn between 3-4 weeks after initiating treatment.
The results need to be reviewed prior to first dose.
17. Subjects with a chronic infection, or a serious infection (infection associated with hospitalization and/or intravenous antibiotics) within 4 weeks prior to investigational product administration.
18. Subjects with active infection at the time of the screening visit and or the first dose visit. Certain minor active infections (ie, vaginitis, tinea, etc) could be allowed on a case-by-case basis only after approval from the Pfizer Physician Clinician.
19. Subject has planned elective surgery during the active dosing period (i.e. Period 1).
20. Subject has received any live vaccines (attenuated vaccine) within 4 weeks prior to first dose.
21. Investigational drugs half-lives of greater than 5 weeks taken less than 6 months prior to first dose.
[For the full list of Exclusion Criteria refer to Section 4.4 of the Protocol]

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-08-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Enbrel
Generic name:	Etanercept
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	11-11-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	05-04-2016
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-04-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	30-10-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2015-000541-24-NL
ClinicalTrials.gov	NCT02509026
CCMO	NL54909.058.15