A Multicentre, 12 Week Double Blind Placebo Controlled Randomized Study of Etanercept on a Background NSAID in the Treatment of Adult Subjects with Non Radiographic Axial Spondyloarthritis with a 92 Week Open Label Extension

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Primary objectiveThe primary objective of this study is to compare the efficacy of ETN against placebo in improving symptoms of early non-radiographic axial SpA at 12 weeks when added to a background NSAID at the optimal anti-inflammatory dose....

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

Summary

ID

NL-OMON38358

Source
ToetsingOnline

Brief title
B1801031-Axial Spondyloarthritis

Condition

- Joint disorders

Synonym
chronic inflammatory disease characterized by joint inflammation

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Axial spondyloarthritis, Etanercept, Phase 3b

Outcome measures

Primary outcome

The primary endpoint of this study is the proportion of subjects who achieve

ASAS 40 at week 12.

Secondary outcome

Secondary endpoints

1. Proportion of subjects who achieve ASAS 40 at time points other than 12

weeks;

2. Proportion of subjects who achieve ASAS 20;

3. Proportion of subjects who achieve ASAS 5/6;

4. Changes from baseline in ASDAS;

5. Proportion of subjects with ASAS partial remission;

6. Time to ASAS partial remission;

7. Changes from baseline in Subject Assessment of Disease Activity (VAS);

8. Changes from baseline in the VAS Physician Global Assessment;

9. Changes from baseline in VAS nocturnal and total back pain over time;

10. Changes from baseline in the BASFI and its components;

11. Changes from baseline in the BASDAI and its components;

12. Proportion of subjects who achieved BASDAI 20 and BASDAI 50;

13. Changes in BAS-G;

14. Changes from baseline in spinal mobility as measured by BASMI (and its individual components), and occiput-to-wall distance, and chest expansion;

15. Changes in inflammation at week 12 as measured by MRI of the spine at week 12;

16. Changes from baseline in tender and swollen joint counts (44 count);

17. Changes from baseline on dactylitis and enthesitis score (MASES);

18. Changes from baseline in the acute phase reactants C Reactive Protein (CRP) and Erythrocyte sedimentation rate (ESR);

19. Health Outcomes Assessments using the following instruments: WPAI, HADS, EQ-5D MFI, SF 36, ASQoL, ASWIS, MOS Sleep, MFI, PASS, and MCII.

Exploratory endpoints

1. Changes from baseline in inflammation of the SI joint at 12 weeks, and in the spine and SI joint at 48 weeks and 104 weeks as measured by MRI;

2. Changes from baseline in spinal x-ray at 104 weeks as measured by mSASSS and RASSS;

Safety Endpoints

1. Safety will be assessed throughout the study. The following variables will be assessed: physical examination, vital signs, hematology, chemistry, lipid profile, urinalysis, premature withdrawal, inflammatory bowel disease (IBD), psoriasis, and eveitis evaluations, adverse events, and serious adverse events

during the study

Study description

Background summary

Axial Spondyloarthritis (AxSpA) is a chronic disease whose most devastating clinical manifestation is the loss of mobility. Commonly AxSpA progresses from sacral inflammation to progressive spine ankylosis over time. Currently there is no cure for AxSpA.
Current standard of care in the treatment of early AxSpA includes therapy with nonsteroidal anti-inflammatory agents (NSAIDs) with the aim of relieving clinical symptoms.
Traditionally NSAIDs are given on an *as needed basis*. However, in a recent study by Wanders, continuous NSAID therapy was found superior to intermittent NSAID use in active established AS with less radiographic progression as assessed over a 2 year period.
To date, besides NSAIDs, there is no single drug therapy that has been shown to modify the structural progression of AxSpA.
Little data exists on the role of anti-TNFs in the treatment of non-radiographic AxSpA, including the effect on prevention of anatomical progression in this early disease stage before significant x-ray abnormalities develop. Recent data from non-clinical and clinical studies suggest that, in earlier stages of the disease, inflammation drives new bone formation. Later in the disease process, inflammation and bone formation might become independent of each other, therefore decreasing inflammation would not be enough to prevent new bone formation, and on the contrary, it might facilitate it. Therefore, it has been hypothesized that the early use of anti-TNFs, before the bone formation process becomes uncoupled from inflammation, might have a beneficial effect on the anatomical progression of AxSpA.

Study objective

Primary objective
The primary objective of this study is to compare the efficacy of ETN against placebo in improving symptoms of early non-radiographic axial SpA at 12 weeks when added to a background NSAID at the optimal anti-inflammatory dose.

Secondary Objectives
1. To assess the efficacy and safety of ETN + background NSAID over 104 weeks;
2. To compare the effect of ETN 50 mg once weekly versus placebo on inflammation seen in MRI of the spine at 12 weeks when added to a background NSAID at the optimal anti-inflammatory dose;
3. To compare the quality of life between those subjects treated with ETN 50 mg

once weekly versus placebo over 12 weeks when added to a background NSAID at the optimal anti-inflammatory dose.

Exploratory Objectives
1. To evaluate the effect of ETN plus background NSAID on radiographic and MRI changes for up to 104 weeks.

Study design

Period 1: 12 Week Double Blind Placebo Controlled Randomized Study
Period 2: Open-label Treatment period for patients who complete the 12 Week Period 1.
This multicentre, double blind, placebo-controlled (Period 1), two period randomized study will evaluate the efficacy of ETN (ETN 50 mg weekly) vs. placebo in the treatment of subjects with active axial spondyloarthritis despite optimal tolerated NSAID therapy and with non-radiographic sacroiliitis defined as those patients who did not meet the modified NY criteria. Approximately 200 eligible subjects will be randomly assigned in a 1:1 ratio to receive either ETN 50 mg subcutaneously (SC) weekly plus a stable background NSAID at optimal anti inflammatory dosage as determined by the investigator, or ETN placebo plus background NSAID for 12 weeks (Period 1) and will be stratified based on positive or negative sacroiliitis on MRI. The use of placebo as a control is necessary to allow a valid comparison and to provide a quantitative assessment of effect. All subjects who complete the 12 week controlled period may enter into a 92 week open-label treatment period with ETN 50 mg once weekly + background NSAID (Period 2). A safety follow-up (V17) will be performed approximately
30 days after the last dose of study medication. This follow up will be done by telephone.

Intervention

Approximately 200 eligible subjects will be randomly assigned in a 1:1 ratio to receive either ETN 50 mg subcutaneously (SC) weekly plus a stable background NSAID at optimal tolerated anti inflammatory dosage as determined by the investigator, or ETN placebo plus background NSAID for 12 weeks (Period 1) and will be stratified based on positive or negative sacroiliitis on MRI. All subjects who complete the 12 week controlled period may enter into a 92 week open-label treatment period with ETN 50 mg once weekly + background NSAID (Period 2).

Study burden and risks

see for the burden and risks for this study: section E9 of the ABR form and the ICF.

Axial Spondyloarthritis (AxSpA) is a chronic disease whose most devastating clinical manifestation is the loss of mobility. Commonly AxSpA progresses from sacral inflammation to progressive spine ankylosis over time. Currently there is no cure for AxSpA.
Current standard of care in the treatment of early AxSpA includes therapy with nonsteroidal anti-inflammatory agents (NSAIDs) with the aim of relieving clinical symptoms.
Traditionally NSAIDs are given on an *as needed basis*. However, in a recent study by Wanders, continuous NSAID therapy was found superior to intermittent NSAID use in active established AS with less radiographic progression as assessed over a 2 year period.
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Little data exists on the role of anti-TNFs in the treatment of non-radiographic AxSpA, including the effect on prevention of anatomical progression in this early disease stage before significant x-ray abnormalities develop. Recent data from non-clinical and clinical studies suggest that, in earlier stages of the disease, inflammation drives new bone formation. Later in the disease process, inflammation and bone formation might become independent of each other, therefore decreasing inflammation would not be enough to prevent new bone formation, and on the contrary, it might facilitate it. Therefore, it has been hypothesized that the early use of anti-TNFs, before the bone formation process becomes uncoupled from inflammation, might have a beneficial effect on the anatomical progression of AxSpA.

Contacts

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Scientific
Pfizer

235 East 42nd Street
New York, NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Diagnosis of axial spondyloarthritis, as defined by the ASAS criteria. Duration of symptoms of >3 months and <5 years at the time of consent (Appendix 1).
2. Active symptoms defined by a BASDAI *4.
3. Axial symptoms of back pain with a less than favorable response to current intake of an NSAID at optimal tolerated dose as determined by the investigator. Subjects must have failed at least 2 NSAIDs (including the current one) taken separately at the optimal tolerated dose with a total combined duration of >4 weeks.
4. Subject must be taking a stable dose of an NSAID for at least 14 days before baseline.
5. Female or male 18 years or older but less than 50 years at the time of consent.
6. In the opinion of the investigator, subject is a reasonable candidate for treatment with etanercept.
7. No contraindication to MRI examination (metal implants or inability to lay flat for 30-60 minutes for example).
8. Negative serum pregnancy test taken at screening, negative urine pregnancy test taken at baseline and serum pregnancy test collected at baseline (Section 4.3 Lifestyle Guidelines).
9. Agreement by male subjects who are not surgically sterile and female subjects who are not surgically sterile or post menopausal to use a highly effective method of birth control for the duration of the study (Section 4.3 Lifestyle Guidelines).
10. Ability to self-inject drug or have a designee who can do so.
11. Ability to store injectable test article under refrigerated conditions.
12. Demonstrates an adequate screening for tuberculosis (TB) in accordance with local country guideline.
13. Subject is able to complete health outcomes assessments and test article diary.

Exclusion criteria

1. Subjects who are investigational site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.
2. 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
3. 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 immunosupressant.
4. Any orthopedic or medical condition that can cause chronic back pain (different than SpA) such as spondylodiscitis, tumor or advance discopathy.
5. Evidence of IBD flare within 6 months of baseline.
6. Evidence of current or recent episodes of uveitis within 6 months of baseline.
7. Radiological sacroiliitis grade is 3-4 unilaterally or grade *2 bilaterally as defined by the NY criteria (Appendix 2).
8. Subject has a known or suspected allergy, hypersensitivity, or contraindication to ETN, its excipients, or other compounds related to this class of medication.
9. Subject has concurrent treatment with more than 1 NSAID within 14 days at baseline.
10. Subject has a dose of NSAID that changed within 14 days before baseline.
11. DMARDS other than methotrexate, sulfasalazine and hydroxychloroquine within 4 weeks of baseline.
12. Subject has had a dose of prednisone >10 mg/day (or equivalent) or has had a dose changed within 4 weeks before baseline.
13. Subject has received an intra-articular, intravenous, intramuscular, or subcutaneous (SC) corticosteroid within 4 weeks before baseline.
14. Subject is a pregnant or breastfeeding woman.
15. Has current or recent (within 2 years of screening) active TB infection.
* Local country guidelines should be followed for appropriate TB screening in the setting of anti-TNF therapy, including a minimum of a chest radiograph and objective TB testing such as purified protein derivative [PPD] or Quantiferon depending on what is acceptable per local guidelines.
16. Untreated latent TB.
* Subjects with known latent TB infection may be allowed only if local guidelines are followed for prophylactic therapy and if TB chemoprophylaxis has been adequately completed or initiated at least 4 weeks prior to screening.
17. Received TB chemoprophylaxis during screening and has had ALT and/or AST >2x upper limit of normal [ULN] during this period.
* For subjects that have been diagnosed with TB and started chemoprophylaxis during the screening period, additional blood samples for ALT and AST must be drawn between 3- 4 weeks after initiating chemoprophylaxis. The results need to be reviewed prior to randomization.
18. Serious infection (infection associated with hospitalization and/or intravenous antibiotics) within 1 month before test article administration.
19. Active infection at the time of the screening visit and/or the baseline visit. Certain minor active infections (ie, vaginitis, tinea, etc) could be allowed on a case by case basis only after approval from the study physician clinician.
20. Participation in other studies with a therapeutic active component within 3 months before the current study begins and/or during study participation. (Participation in non-interventional or retrospective studies might be permitted following consultation with the Pfizer Clinical team.)
21. Planned elective surgery during Period 1.
22. Subject received any live vaccines (attenuated vaccines) within 4 weeks before baseline.
23. Subject is illiterate.
24. Subject has an abnormal hematology or blood chemistry profile during the screening period. Refer to Section 6.6 for management of exclusionary lab values at baseline.

* White blood cell (WBC) count *3.5 x 109/L;
* Hemoglobin level *85 g/L or *5.3 mmol/L;
* Hematocrit *27%;
* Platelet count *125 x 109/L;
* Serum creatinine level *175 µmol/L (*1.98 mg/dL);
* Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level *2 times the laboratory*s upper limit of normal.
25. Subject has any clinically relevant concurrent medical conditions, including:
* Known history or presence of acute or chronic hepatitis B or hepatitis C or HIV infection; (If required by Health Authorities, an HIV test must be performed at a local lab during screening. Results of this test will be used to determine eligibility.)
* Uncompensated congestive heart failure, or class III or IV heart failure defined by the New York Heart Association classification;
* Uncontrolled hypertension (defined as screening systolic blood pressure >160 mm Hg or screening diastolic blood pressure >100 mm Hg);
* Myocardial infarction within 12 months before the screening visit;
* Coronary artery by pass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within 12 months before the baseline visit;
* Unstable angina pectoris within 6 months before the screening visit;
* Severe pulmonary disease requiring recurrent hospitalizations or supplemental oxygen;
* Presence or history of confirmed blood dyscrasias;
* Diagnosis of multiple sclerosis or other central or peripheral nervous system demyelinating diseases;
* Presence or history of cancer (or carcinoma in situ) other than resected cutaneous basal cell or squamous cell carcinoma;
* Uncontrolled diabetes mellitus;
* Diagnosis of rheumatoid arthritis, systemic lupus erythematosus, scleroderma, or polymyositis;
* Open cutaneous ulcers;
* Liver cirrhosis or fibrosis;
* Other severe acute or chronic medical or psychiatric condition, substance abuse or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this 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):	07-12-2011
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	enbrel
Generic name:	etanercept
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-05-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-01-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2012

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2010-020077-16-NL
ClinicalTrials.gov	NCT01258738
CCMO	NL34736.018.11