A Multicenter, Randomized, Double-Blind, Study Comparing the Efficacy and Safety of Continuing Versus Withdrawing Adalimumab Therapy in Maintaining Remission in Subjects with Non Radiographic Axial Spondyloarthritis

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The objective of this study is to evaluate the efficacy and safety of continuing versus withdrawing therapy with adalimumab 40 mg given every other week (eow) SC in maintaining remission in subjects with nr-axSpA.

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

Summary

ID

NL-OMON41245

Source
ToetsingOnline

Brief title
M13-375 Spondyloarthritis study

Condition

- Autoimmune disorders
- Joint disorders

Synonym
Axial spine arthritis, inflammation of the spine and joints

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie B.V.
Source(s) of monetary or material Support: AbbVie

Intervention

Keyword: Adalimumab, non-radiographic axial spondyloarthritis, remission

Outcome measures

Primary outcome

Primary Efficacy Variable

The primary efficacy variable is the proportion of subjects who do not

experience a flare during Period 2 by Week 68 of the study where a flare is

defined as having any 2 consecutive study visits with ASDAS * 2.1.

Secondary outcome

Secondary efficacy variables include the following:

At 12 Weeks after Initiation of Rescue Therapy:

* ASDAS Inactive Disease (ASDAS < 1.3)

* ASDAS Major Improvement (a change from baseline * *2.00)

* ASDAS Clinically Important Improvement (a change from baseline * *1.10)

* ASAS20, ASAS40, ASAS 5/6 and ASAS Partial Remission

* ASAS20 response: improvement of * 20% and absolute improvement of * 1

unit (on a scale of 0 to 10) from Baseline in * 3 of the following 4 domains:

* Patient's Global Assessment

* Pain

* Function

* Inflammation

* ASAS40 response: improvement of * 40% and absolute improvement of * 2 units (on a scale of 0 to 10) from Baseline in * 3 of the 4 domains above in ASAS20 with no deterioration in the potential remaining domain

* ASAS partial remission: absolute score of < 2 units for each of the 4 domains identified above in ASAS20

* ASAS 5/6 response: 20% improvement from Baseline in 5 out of the following 6 domains: BASFI, patient's assessment of total back pain, PTGA-disease activity, inflammation, lateral lumbar flexion from BASMI, and hs-CRP

* Bath AS Disease Activity Index 50 (BASDAI50)

* Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S)

At Week 28 and Week 68

* ASDAS Inactive Disease

* ASDAS Major Improvement

* ASDAS Clinically Important Improvement

* ASAS20, ASAS40, ASAS 5/6 and ASAS Partial Remission

* BASDAI50

* HAQ-S

At Week 68

* Time to flare defined as ASDAS * 2.1 at 2 consecutive visits

* Time to partial flare defined as ASDAS * 1.3 but < 2.1 at 2 consecutive visits

* Proportion of subjects who reach flare definition

* Proportion of subjects who reach partial flare definition

See also protocol page 70.

Study description

Background summary

There is a medical need for treatment in nr-axSpA patients who fail nonsteroidal anti-inflammatory drug (NSAIDs). Clinical trial data indicate that AS and nr-axSpA patients have comparable burden of disease that requires treatment irrespective
of radiographic progression. NSAIDs are considered first line therapy for all axial SpA patients. Traditional disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) and sulfasalazine (SSZ) have not been shown to be effective for axial SpA.
For AS and nr-axSpA patients who continue to have active disease despite NSAIDs, adalimumab is an approved therapy.

Study objective

The objective of this study is to evaluate the efficacy and safety of continuing versus withdrawing therapy with adalimumab 40 mg given every other week (eow) SC in maintaining remission in subjects with nr-axSpA.

Study design

This clinical trial was designed to evaluate the efficacy and safety of adalimumab 40 mg every other week (eow) versus placebo in maintaining remission in patients with nr-axSpA.
Based on past clinical trials of adalimumab in AS and in nr-axSpA patients, 28 weeks of adalimumab treatment in Period 1 is expected to be sufficient to identify most subjects who will respond and achieve remission (ASDAS Inactive Disease) with this therapy.

In Period 2, patients who achieve remission after period 1, are randomized to receive either blinded adalimumab or placebo.
The primary endpoint will be the proportion of subjects who do not experience a

flare by Week 68.
The proposed 40-week duration of the double blind period is based on results of 2 prior trials that demonstrated the occurrence of disease flare in patients taken off adalimumab and other anti TNF therapy.

The study duration will include a 30-day Screening Period, a 28-week open-label (OL) 40 mg adalimumab eow treatment period (Period 1), a 40 week double-blind placebo controlled eow treatment period (Period 2). There is an opportunity to receive at least 12 weeks of rescue therapy depending on the remission or flare status.
A 70-day follow-up phone call will be performed.
Length of exposure will be maximal 80 weeks of treatment.

Intervention

Open-Label * Period 1
Starting on Day 1 through Week 26, subjects will be administered open label adalimumab 40 mg every other week (eow).
Drug will be subcutaneously self-administered or administered by a qualified designee every other week at approximately the same time of day.
Subjects will be discontinued from the study if they do not meet the ASDAS remission criteria on week 20, 24 and 28.
Subjects meeting the criteria will be randomized 1:1 to receive either blinded adalimumab 40 mg eow or matching placebo.

Double-Blind * Period 2
Starting at Week 28, subjects who are eligible for randomization into Period 2 will receive the first dose of blinded study drug (adalimumab 40 mg eow or placebo).

Rescue Therapy During Period 2
Starting at Week 36, subjects who meet the flare criteria (flare is defined as 2 consecutive study visits with ASDAS * 2.1) will be given rescue therapy with open-label adalimumab 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of the study. For subjects who meet the flare criteria at Weeks 60, 64 or 68, rescue therapy with open label adalimumab 40 mg eow will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80, respectively.

Study burden and risks

Benefits and Risks
There is a medical need for the treatment of nr-axSpA. The utility of TNF blockade with adalimumab in nr-axSpA has been established in a randomized controlled trial which demonstrated a safety profile similar to that observed in the extensive clinical and post-marketing experience of adalimumab in a wide

range of disease states including the associated indication of AS. The safety profile of adalimumab in this and other approved indications is well established. Adverse events in the categories of autoimmunity, demyelinating disorders, congestive heart failure, gastrointestinal disorders, hematologic events, hepatic events, hypersensitivity, immunosuppression, infections, malignancies, respiratory thoracic and mediastinal disorders, and vascular disorders have been observed with adalimumab therapy.
For Study M13-375, to ensure nr-axSpA subjects are appropriate candidates for anti-TNF therapy, subjects are required to meet a minimum level of disease activity at baseline (ASDAS * 2.1, BASDAI * 4, Patient's Assessment of Total Back Pain score * 4), have objective evidence of active disease (inflammation in the SI joints or spine on MRI or elevated hs-CRP), and have had an inadequate response to at least 2 NSAIDs or a contraindication or intolerance to NSAIDs. Further detailed information regarding potential risks and benefits of adalimumab can be found in the Investigator's Brochure.

The potential benefit of the proposed study in nr-axSpA is that it is designed to evaluate the efficacy and safety of continuing versus withdrawing therapy with adalimumab 40 mg given eow SC in maintaining remission in subjects with nr-axSpA. As nr-axSpA is associated with considerable pain, reduction in health-related quality of life, and work impairment, it would benefit patients to know if persistent adalimumab therapy is required to maintain remission.

Contacts

Public
AbbVie B.V.

Wegalaan 9
Hoofddorp 2132 JD
NL
Scientific
AbbVie B.V.

Wegalaan 9
Hoofddorp 2132 JD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Main Inclusion: ;- Adult subjects with inadequate response of 2 or more non-steroidal anti-inflammatories (NSAIDs);- Subject with axial SpA fulfilling the Assessment of Spondyloarthritis International Society (ASAS) axial SpA classification criteria ;- Subject with evidence of active inflammation in the SI joints or spine on MRI, or elevated hs-CRP;- Negative purified protein derivative (PPD) test and Chest X-Ray performed at Baseline Visit must be Negative;- Negative TB screening assessment;- Ability to administer subcutaneous injections;- General good health otherwise

Exclusion criteria

Main Exclusion: ;- Prior anti-TNF therapy;- Fulfillment of modified New York criteria for Ankylosing Spondylitis;- Recent infection requiring treatment;- Significant medical events or conditions that may put patients at risk for participation;- Female subjects who are pregnant or breast-feeding or considering becoming pregnant during the study;- History of cancer, except successfully treated skin cancer;- Recent history of drug or alcohol abuse

Study design

Design

Study phase:	4
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):	19-08-2013
Enrollment:	54
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Humira
Generic name:	Adalimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	17-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	18-06-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	06-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	04-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2015
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	EUCTR2012-000646-35-NL
ClinicalTrials.gov	NCT018008118

Register	ID
CCMO	NL44066.018.13