A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING STUDY OF THE EFFICACY AND SAFETY OF TOFACITINIB IN SUBJECTS WITH ACTIVE ANKYLOSING SPONDYLITIS (AS)

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1. To compare the efficacy of tofacitinib, in doses of 2 mg, 5 mg, and 10 mg BID versus placebo on the ASAS20 response rate at Week 12 in subjects with active AS that have had an inadequate response to previous treatment.2. To estimate the placebo-...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON40951

Source
ToetsingOnline

Brief title
A3921119 (9002/0151)

Condition

- Autoimmune disorders
- Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)

Synonym
Ankylosing spondylitis, Bechterew's disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Ankylosing Spondylitis, double-blind, Phase 2, placebo-controlled trial, Randomized, Tofacitinib

Outcome measures

Primary outcome

Primary Efficacy Endpoint: ASAS 20 response rate at 12 weeks of treatment.

Secondary outcome

Secondary Efficacy Endpoints:

- A validated endpoint such as Spondyloarthritis Research Consortium of Canada (SPARCC) Magnetic Resonance Imaging (MRI) Index of Disease Activity Score and/or modified Berlin Ankylosing Spondylitis Spine Magnetic Resonance Imaging Activity Score (ASspiMRI) of the SI joints and spine at Week 12.

- ASAS20 response at all other time points, ASAS40 response, ASAS 5/6 response at all time points.

- Ankylosing Spondylitis Disease Activity Score using C-Reactive Protein (ASDASCRP) at all time points.

- ASDAS clinically important improvement, ASDAS major improvement and ASDAS inactive disease at all time points.

- BASDAI, BASDAI50 response, BASFI, BASMI at all time points.

- Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at all time points

collected.

- Extra-articular involvement at all time points collected.

- Spinal mobility at all time points collected.

Quality of Life Endpoints:

- Short-Form-36 Health Survey (SF-36) Version 2, Acute at all time points collected.

- EuroQol EQ-5D Health State Profile (EQ-5D) at all time points collected.

- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at all time points.

Safety Endpoints:

- Incidence and severity of Adverse Events (AE).

Other Endpoints:

- ASAS partial remission criteria at all time points.

- Fluorescence Activated Cell Sorting (FACS) analysis of lymphocyte subsets.

- Ankylosing Spondylitis Quality of Life (ASQoL) at all time points collected.

- Work Productivity and Activity Impairment (WPAI) Questionnaire: Spondyloarthritis at all time points collected.

- AS HealthCare Resource Utilization Questionnaire (AS-HCRU) at all time points collected.

- Clinical laboratory tests, vital signs, physical examination and 12-lead ECG parameters.

- Oral clearance (CL/F) and other pharmacokinetic (PK) parameters calculated

from plasma tofacitinib concentrations.

Study description

Background summary

Ankylosing Spondylitis (AS) is the most prevalent spondyloarthritis, a group of arthritic conditions affecting the spine. This under recognized disease is often not diagnosed for many years and typically presents in people between 20 and 40 years of age leading to progressive disability and adverse effects on quality of life. Tofacitinib inhibits signaling of cytokines that are integral to lymphocyte activation, proliferation, and function and may thus result in suppression of multiple aspects of the immune response. This forms the basis of the rationale to investigate the effect of tofacitinib in active AS.

This study represents the first investigation of tofacitinib in subjects with ankylosing spondylitis. It is designed to obtain more information on the safety, pharmacokinetics and clinical efficacy in this population prior to advancing to large clinical trials. This study will also provide critical information for the design of future tofacitinib studies in the AS population.

Study objective

1. To compare the efficacy of tofacitinib, in doses of 2 mg, 5 mg, and 10 mg BID versus placebo on the ASAS20 response rate at Week 12 in subjects with active AS that have had an inadequate response to previous treatment.
2. To estimate the placebo-corrected dose response for the ASAS20 at Week 12 in subjects with active AS that have had an inadequate response to previous treatment.
3. To compare the safety of tofacitinib at all doses versus placebo in all study subjects.

Study design

This is a Phase 2b, multicenter, randomized, double blind, placebo controlled dose ranging, parallel group efficacy and safety study designed to characterize the dose response of tofacitinib in subjects with active AS. An estimate of approximately 300 AS subjects will be screened globally in order that approximately 200 eligible subjects (50 per arm) will be randomized. Active disease is required for entry into this study and is defined as: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of >=4 and back pain score (BASDAI Question 2) of >=4 despite treatment with NSAIDS (or

intolerance to NSAIDs). Subjects will be randomized at the Baseline visit in a 1:1:1:1 ratio to one of four treatment sequences for a total of 12 weeks of treatment.

Intervention

Subjects will be randomized 1:1:1:1 to one of four treatment arms;
1. Tofacitinib 2 mg BID
2. Tofacitinib 5 mg BID
3. Tofacitinib 10 mg BID
4. Placebo BID

Study burden and risks

Potential Benefits
Given the chronic nature of this disorder and the limited available therapies, there remains an unmet medical need for an effective oral treatment for AS. The benefits to individual subjects participating in this study will be the potential control of the disease activity by improving signs and symptoms. All subjects may also benefit from gaining knowledge about their health status through study tests and physician assessments, as well as having close monitoring of their disease. If proof-of-concept is established in this study and the product moves to Phase 3, subjects participating in this study may be eligible to enter the future open-label extension study.

Potential Risks
The risks associated with tofacitinib are similar to the risks associated with the use of other immunosuppressive agents, including a potential increased risk for serious and other important infections, including tuberculosis and viral reactivation such as herpes zoster. In RA subjects who have received tofacitinib, the rate of serious infections is higher in subjects 65 years of age and older. Decreases in white blood cell counts, particularly neutrophils and lymphocytes, and decreases in hemoglobin have been observed. These effects were usually mild to moderate and returned to normal after discontinuation of therapy. Treatment with tofacitinib was associated with increases in levels of LDL and HDL cholesterol, with the ratios of mean LDL/HDL cholesterol unchanged. In the previous controlled trials, elevation of LDL cholesterol generally returned to pre-treatment levels after discontinuation of tofacitinib. Review of cardiovascular events reported in the RA studies suggests that tofacitinib does not appear to increase cardiovascular risk in subjects with RA during both short- and long-term treatment. The long-term implications of these changes for cardiovascular risk are currently unknown.

Also seen in previous studies were slight increases in measured serum creatinine and serum transaminases. This effect generally returned to normal after discontinuation of therapy. A single RA subject experienced possible

drug-induced liver injury (DILI) while being treated with tofacitinib and methotrexate. Tofacitinib was discontinued and she recovered following treatment with prednisone and azathioprine. The time course of her biochemical abnormalities were atypical for DILI, however investigations did not reveal an alternative etiology. Infections, anemia and neutropenia are all consistent with the pharmacology of tofacitinib as a potent inhibitor of JAK3 with cross-over to JAK1 and moderate selectivity for JAK2. Potential risks that may also be associated with the use of tofacitinib include a potential increased risk of lymphoma and lymphoproliferative disorders, and other malignancies.

Cases of gastrointestinal (GI) perforation were observed in RA subjects taking tofacitinib, often in the setting of diverticulitis. All affected subjects were taking concomitant NSAIDs and/or corticosteroids that have been associated with an increased risk of GI tract injury. Isolated events of gastrointestinal perforation have also been reported in clinical trials in psoriasis and renal transplant subjects. These trials are still blinded, but at least one subject received tofacitinib. These perforations were reported as diverticulitis or perforated diverticulum. In one report, the perforation occurred approximately two weeks after discontinuation of study therapy. Based on nonclinical data, there is a potential risk for teratogenicity with tofacitinib. A more detailed discussion for tofacitinib can be found in the Investigator*s Brochure.

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. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) 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. Subject is at least 18 years old (20 years old for subjects in Taiwan) at the Screening Visit. ;4. The subject has a diagnosis of AS based on the Modified New York Criteria for Ankylosing Spondylitis (1984). ;5. Subject has active AS at the Screening and Baseline (Day 1) visits defined as:;• BASDAI score of >=4; and;• Back pain score (BASDAI Question 2) of >=4.;6. Subject has active disease despite nonsteroidal anti-inflammatory drug (NSAID) therapy or is intolerant to NSAIDs as defined by either:;- Subject must have had an adequate trial of at least 2 different oral NSAIDs taken over a total period of 4 weeks. ;or;- Intolerance to NSAID therapy. Intolerance is defined as the subject must have discontinued NSAID treatment due to a related adverse event (eg, allergic reaction, gastrointestinal symptoms or signs, hypertension, etc).;7. Subjects may be receiving the following non-biologic DMARDs at the time of the Screening visit. These medications should be continued throughout the entire study and doses should remain unchanged. Any other DMARDs require discussion prior to enrollment with the sponsor for washout timeframe.;• Methotrexate: Maximum dose of 20 mg/week. Minimum duration of therapy 4 months and dose stable for 4 weeks prior to first dose of study drug. Subjects on methotrexate should be on an adequate and stable dose of folate supplementation (eg, not less than 5 mg weekly based on folic acid, unless such doses would violate the local label guidelines or standard of care) for at least 4 weeks prior to the first dose of study drug. Subject must not have had previous serious toxicity while on;methotrexate and not be expected to require evaluation for possible methotrexate toxicity (eg, require a liver biopsy for methotrexate toxicity) during the study; • Sulfasalazine (Azulfidine, Salazpyrin): Maximum dose of 3 gm/day. Minimum duration of therapy 2 months and dose stable for 4 weeks prior to first dose of study drug.;8. Subjects who are already taking oral corticosteroids (not injectables) may participate in the study:;• Oral corticosteroids: Subjects who are already receiving oral corticosteroids must be;on a stable dose of <=10 mg/day of prednisone or equivalent for 4 weeks prior to the first dose of study medication;;• Injected (eg, intraarticular, intramuscular, epidural or intravenous) corticosteroids;must be discontinued 4 weeks prior to the first dose of study medication;;• Topical and intra-rectal corticosteroids will be allowed during the study.;9. Subject has discontinued all disallowed concomitant medication for the required time prior to the first dose of study medication and is taking only those concomitant medications in doses and frequency allowed by the protocol.;10. Subjects who are receiving any investigational or marketed treatment for AS, arthritis or back pain not mentioned elsewhere must have that treatment discontinued for 4 weeks or 5 half-lives, whichever is longer.;11. Subjects receiving non-prohibited concomitant medications for any reason must be willing to stay on a stable

regimen as defined in the protocol. ;12. No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined in protocol. ;13. Women of childbearing potential must test negative for pregnancy prior to enrollment in this study. ;15. Female subjects who are not of childbearing potential (ie, meet at least one of the following criteria): • Have undergone hysterectomy or bilateral oophorectomy; • Have medically confirmed ovarian failure; • Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause); laboratory confirmation of FSH level indicative of post menopausal according to the central laboratory may be indicated per investigator*s determination.

Exclusion criteria

1. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial. ;2. Participation in other interventional studies within 4 weeks before the current study begins and/or during study participation (excluding noninterventional follow-up during the screening period). ;3. Subjects receiving any other DMARDs (other than those allowed), thalidomide (including previous use).;4. Subjects currently receiving or previous use of a TNF inhibitor or other biological agent. ;5. Blood dyscrasias at screening or within 3 months prior to the first dose of study drug including confirmed:;a. Hemoglobin <= g/dL;;b. Absolute white blood cell count (WBC) <=3.0 x 10 9/L (<=3000 mm3);;c. Absolute neutrophil count (ANC) <=1.2 x 10 9/L (<= 1200 mm3);;d. Absolute lymphocyte count <= 1.0 x 10 9/L (<= 1000/mm3);;e. Platelet count <=100 x 10 9/L (<=100,000/mm3).;One re-testing of a laboratory-acceptable specimen (eg, appropriately labeled within stability parameters, not hemolyzed, appripriate type (tube and reagent) and volume) is allowed of any above parameters if the abnormal lab(s) was an uncharacteristic result(s). Documentation in the source of the typical results to allow a repeat lab is required.;Re-test must be completed within the screening period.;6. Estimated Creatinine Clearance <=40 mL/min based on Cockcroft Gault equation at Screening visit. ;7. Total bilirubin, AST or ALT more than 1.5 times the upper limit of normal at screening visit. (One re-testing with an uncompromised sample is allowed if the abnormal lab result was an uncharacteristic result and must be completed within the screening period. Documentation in the source of the typical results to allow a repeat lab is required).;8. History of any other autoimmune rheumatic disease (eg, systemic lupus erythematosis (SLE), mixed connective tissue disease (MCTD), scleroderma, polymositis) or known diagnosis of fibromyalgia, without approval by Sponsor. ;9. History of an infected joint prosthesis at any time, with the prosthesis still in situ. ;10. History of any lymphoproliferative disorder, such as Epstein Barr Virus related;lymphoproliferative disorder (EBV-LPD), history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.;11. History of recurrent (more than one episode) herpes zoster or disseminated/multi-dermatomal (a single episode) herpes zoster or disseminated (a single episode) herpes simplex. ;12. History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study medication.;13. History of infection requiring antimicrobial therapy within 2 weeks prior to the first dose of study medication. ;14. Any prior treatment with alkylating agents (eg, cyclophosphamide or chlorambucil), total lymphoid

irradiation, etc. 15. Any subject who has been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study medication or is to be vaccinate with these vaccines at any time during treatment or within 6 weeks after last dose of study drug.;16. A subject with any condition possibly affecting oral drug absorption, eg, gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding, that simply divide the stomach into separate chambers, are NOT exclusionary. 17. History of alcohol or drug abuse unless in full remission for greater than 6 months prior to first dose of study medication.;18. Body weight or body habitus greater than what can be accommodated by the site*s MRI scanner table weight limits or MRI scanner bore.;19. Any contraindication to MRI that in the judgment of the investigator and MRI center poses a safety risk to the subject such as, but not limited to, cardiac pacemaker; implanted cardiac defibrillator; aneurysm clips; carotid artery vascular clamp; neurostimulator; insulin or infusion pumps; bone growth/fusion stimulator; cochlear, otologic, and ear implants. ;20. Subjects with passive implants that may be weakly ferromagnetic in the vicinity of the RF coil that may cause image artifacts in the spine and SI joints. ;For exclusion criteria 21-30 see protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Tofacitinib

Generic name:	Tofacitinib

Ethics review

Approved WMO Date:	23-06-2014
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	01-09-2014
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	16-10-2014
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)

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	EUCTR2011-005689-39-NL
ClinicalTrials.gov	NCT01786668
CCMO	NL49618.048.14