A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of VX-509 using Magnetic Resonance Imaging and Arthroscopic Biopsies in Subjects with Active Rheumatoid Arthritis on Stable Disease-Modifying Antirheumatic Drugs

Published: 27-03-2013
Last updated: 25-04-2024

1.1 Primary ObjectivesDuring 12 weeks of treatment in subjects with active RA on stable DMARD therapy:• To evaluate the efficacy of VX-509 across a range of doses• To evaluate the early effect of VX-509 administration on joint structures as assessed…

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

Summary

ID

NL-OMON40008

Source
ToetsingOnline

Brief title
VX12-509-103

Condition

- Joint disorders

Synonym
Active Rheumatoid Arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Vertex Pharmaceuticals
Source(s) of monetary or material Support: Industry: Vertex Pharmaceutical Inc.;is the sponsor of this trial

Intervention

Keyword: Active Rheumatoid Arthritis

Outcome measures

Primary outcome

8.1 Primary Endpoints

* Proportion of subjects who achieve >=20% improvement in disease severity

according to the American College of Rheumatology criteria (ACR20), using

C-reactive protein (CRP) (ACR20-CRP) at Week 12.

* Change from baseline in Disease Activity Score 28 using CRP (4-component)

(DAS28-CRP) at Week 12.

* Change from baseline in OMERACT RAMRIS synovitis score in designated

hand(minimal assessed joints: wrist, MCP joints #2 to #5) at Week 12.

* Change from baseline in OMERACT RAMRIS bone marrow edema (osteitis) in

designated hand (minimal assessed joints: wrist, MCP joints #2 to #5) at Week

12.

* Change from baseline in OMERACT RAMRIS erosion score in designated hand

(minimal assessed joints: wrist, MCP joints #2 to #5) at Week 12.

Secondary outcome

8.2 Secondary endpoints

* Proportion of subjects who achieve ACR50-CRP and ACR70-CRP responses at Week 12.

* Proportion of subjects with DAS28-CRP <2.6, and those who achieve a remission, moderate response or good response according to the European League Against Rheumatism (EULAR) response criteria at Week 12.

* ACR hybrid scores at Week 12.

* Change from baseline in the rheumatoid arthritis quality of life (RAQoL) questionnaire at week 12.

* Change from baseline in OMERACT RAMRIS synovitis, bone marrow edema (osteitis), erosion scores at Week 6.

* PK parameters of VX-509 and its metabolite in plasma (maximum observed concentration [Cmax] and area under the concentration versus time curve [AUC]).

* Safety and tolerability as indicated by adverse events, laboratory tests, electrocardiograms (ECGs) and vital signs.

8.3 Other Endpoints

* Predictive value of RAMRIS responses at Weeks 6 and 12 on DAS28-4(CRP) and ACR20-CRP at Week 12.

* Change from baseline in OMERACT RAMRIS joint space narrowing score at Weeks 6 and 12.

* Change from baseline in the Clinical Disease Activity Index (CDAI), CDAI

moderate and low disease activity, and CDAI remission at Week 12.

* Change from baseline in the remaining 7 subscales of the SF-36 at Week 12.

* Change from baseline in blood biomarkers including markers of bone turnover, cytokines, and other biomarkers.

* Proportion of subjects who achieve ACR20, ACR50, and ACR70 assessed using erythrocyte sedimentation rate (ACR20-ESR, ACR50-ESR, and ACR70-ESR) responses, at Weeks 6 and 12.

* PK/PD relationship for plasma PK parameters and arthritis efficacy including RAMRIS, safety and plasma biomarkers.

Study description

Background summary

VX 509 is a potent small molecule inhibitor of JAK3 in development as a potential treatment for subjects with active RA and other autoimmune diseases. In Phase 2a Study VX09 509 101 (Study 101), VX 509 demonstrated significant activity in reducing signs and symptoms of RA over 12 weeks in subjects not receiving concurrent DMARDs.
Additionally, other generalized JAK inhibitors are in development for RA. Findings from these studies resulted in rapid, statistically significant reductions in the signs and symptoms of RA; however, the effect on progression of erosive disease at 24 weeks in a study with a placebo control arm for 3 months was uncertain ($P<0.05$ with significant contribution by outliers).
The VX 509 Investigator's Brochure provides specific details about the completed nonclinical and clinical VX 509 studies and a full description of safety findings. No safety issues have been identified in studies in RA patients and normal healthy volunteers that would preclude the dosing regimens proposed for the present study; however, this study is the first study in RA subjects receiving a DMARD to evaluate concurrent treatment with VX 509 300 mg daily (qd) for 12 weeks.

Study objective

1.1 Primary Objectives
During 12 weeks of treatment in subjects with active RA on stable DMARD therapy:

• To evaluate the efficacy of VX-509 across a range of doses
• To evaluate the early effect of VX-509 administration on joint structures as assessed by MRI

1.2 Secondary Objectives

During 12 weeks of treatment in subjects with active RA on stable DMARD therapy:

• To evaluate major arthritis improvement with VX-509 administration across a range of doses
• To evaluate changes in RA physical function
• To evaluate changes in physical and mental health-related quality of life
• To investigate the pharmacokinetics (PK) of VX-509 and its metabolite in plasma
• To evaluate the safety of VX-509

1.3 Other Objectives

During 12 weeks of treatment in subjects with active RA on stable DMARD therapy:

• To evaluate the predictive value of MRI response for other efficacy parameters
• To evaluate change in health-related quality of life
• To investigate biomarkers reflecting bone turnover and inflammation during VX-509 administration
• To determine the PK/pharmacodynamic (PD) relationships between plasma exposure to VX-509 and its metabolite and efficacy, safety, and plasma biomarkers

Study design

The study is designed to evaluate early response to VX-509 administration, including local synovial and bone response assessment by MRI imaging (Section 6.5 of the protocol). The double-blind placebo-controlled design will allow comparison to variability in efficacy parameters for control subjects. No blinded joint assessor is utilized in the trial due to the small subject numbers and partial unblinding of all arthroscopy subjects, who are randomized to the 200 mg qd dose of VX-509 (Arm C) to avoid the variability inherent with doseranging.

Due to the increased assay sensitivity of joint MRI, and blinded reading by 2 central readers, there is improved study power to detect RAMRIS differences and the validity of MRI data is maintained. As a sensitivity analysis, the ACR20-CRP and DAS28-4(CRP) efficacy parameters will be re-evaluated without inclusion of the arthroscopy subjects.

Intervention

study medication VX12-509

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness
VX-509, an inhibitor of Janus kinase 3 (JAK3), is developed to treat active rheumatoid arthritis. This study is being done to learn more about the safety and effects of VX-509 on people with RA. The sponsor will also look at how VX-509 may affect the patients* body and how their body breaks down and eliminates VX-509.
The patients will be monitored for possible side effects during the study.
The risks identified based on clinical trials are:

- Headache
- Nausea
- serious infections
- Mild increases of liver enzymes, which could mean inflammation in the liver
- Increase of lipids level
- No studies have been performed to assess any potential risk of cancer

Potential risks identified based on non-clinical studies:
- In a study where animals were dosed with VX-509 for 6 months, abnormalities of the uterus and mammary glands (an organ that produces milk) were noted. In these animals, a hormone known as prolactin is important for uterine and mammary gland function. Due to VX-509, prolactin may not act normally in these animals. In humans, prolactin has different functions, mostly for lactation (secretion of milk) but not on the uterus.
Risks from Withdrawal of Regular Medicines:
- There are certain medicines that patients cannot take while they are in the Study and they may have to stop taking a medicine that they normally take while they are in the Study. The study doctor may decide it is best for the patient to be put back on their regular medicine(s).

Risks Related to Study Tests:
- Blood sample collection: discomfort, pain where the blood is taken, dizziness, infection (rare), bleeding, redness, or bruising at the skin puncture.
- Electrocardiogram (ECG): The sticky pads used for this test may cause skin irritation, discomfort when the sticky pads id taken off
- Chest X-ray / Hand & Foot X-rays: Total amount of radiation from a chest X-ray that each patient will receive in this study is approximately equal to 3 days of exposure of this natural radiation. The radiation from the hand and foot X-ray is much less.
- MRI: Some patients could have a history of allergy or sensitivity to contrast dye, therefore this should be told to the study doctor

Reproductive Risks :
- Patients should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while in this study.

Drug Interaction Risks (medicines working with or against each other):
- The combination of Study Drug and any of these other medications could be harmful to patients.
- VX-509 can decrease the metabolism (breakdown) of other medications that patients may be on and hence increase their levels within their body. This may result in possible side effects associated with those drugs. Patients must not eat/drink grapefruit, grapefruit juice or take St. John's Wort during the Study. Other drugs which strongly block a drug breakdown pathway called CYP3A are not allowed during the study.
Unknown Risks:

There may be side effects that are not yet known.

Contacts

Public
Vertex Pharmaceuticals

130 Waverly St
Cambridge, MA 02139
US
Scientific
Vertex Pharmaceuticals

130 Waverly St
Cambridge, MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Male and female subjects 18 to 65 years of age (inclusive)
• Diagnosis of RA
• Subject must have a swollen joint count of >=6 out of 66 assessed joints and a tender joint count of >=8 out of 68 assessed joints
• Seropositivity based on either a positive rheumatoid factor or anti-cyclic citrullinated peptide antibody at screening OR known erosive disease based on previous X-ray report (available and filed) or erosions detected on baseline hand and foot X-ray
• Baseline CRP level >=1.2 □x ULN or Westergren erythrocyte sedimentation rate >=1.2 x upper limit of normal at screening
• Subjects must be receiving stable therapy with 1 of the following DMARDs: methotrexate, sulfasalazine, leflunomide, anti-malarial drug, or penicillamine.
• Subjects must have palpable 2+ synovitis of the wrist or >=2 MCPs, defined as loss of bony contours with palpable joint effusion and/or swelling, in the MRI-designated hand (the hand being used in MRI assessments).

Exclusion criteria

A complete list of the exclusion criteria can also be found in the protocol Section 10.2 Exclusion Criteria.;Subjects who meet any of the following exclusion criteria will not be eligible for this study:
1. Inflammatory and rheumatological disorders other than RA, where arthritis may be a prominent feature, such as systemic lupus erythematosus, mixed connective tissue disease, scleroderma, poly/dermatomyositis, or gout; secondary Sjogren*s syndrome or interstitial lung disease are allowed.
2. History of any illness that might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This may include, but is not limited to, history of cardiovascular or central nervous system disease, history or presence of clinically significant abnormalities on physical exam, ECG or laboratory examination, or history of clinically significant psychiatric or mental disease.
3. History of cancer, except squamous or basal cell cancers of the skin or in situ cancer of the cervix.
4. History of hematologic disorders including neutropenia and thrombocytopenia other than Felty*s syndrome.
5. History of tuberculosis (TB), regardless of history of anti-mycobacterial treatment; or active TB as determined by X-ray, TB skin test and QuantiFeron® TB Gold Assay (QuantiFeron assay). If the subject has a hypersensitivity to skin test preparation associated with the TB skin test then the QuantiFeron alone is acceptable.
6. Acute or chronic active infection requiring systemic antimicrobial treatment with the exception of onychomycosis receiving antifungal medication, or acne and rosacea receiving low-dose antibiotics.
7. History of febrile illness within 5 days before the first dose of study drug.
8. History of previous osteomyelitis, infected joint or joint prosthesis.

9. Subjects who are at high risk of developing an infection due to a compromised immune system including poorly controlled diabetes.
10. Weight <45 kg at screening.
11. A 12-lead ECG demonstrating QT interval corrected (QTc) >450 msec at the screening Visit. If QTc exceeds 450 msec, the ECG should be repeated 2 more times, and the average of the 3 QTc values used to determine the subject*s eligibility. Subjects should also be excluded if any other clinically significant interval (e.g., PR prolongation), morphologic (e.g., T-wave inversion), or conduction abnormalities are observed.
12. Planned surgery during the study.
13. Metal implant or other contra-indication to MRI scanning.
14. History of alcohol or drug abuse, or excessive alcohol consumption as determined by the investigator, during the previous 12 months before screening.
15. For female subjects: Pregnant or nursing; or planning to become pregnant during the study or within 90 days following the last VX-509 dose; or female subjects of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined in this protocol from at least 14 days before the first dose of study drug and for 90 days following the last dose of study drug.
16. For male subjects: Subject has a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days following the last VX-509 dose; or male subjects who are unwilling or unable to use an acceptable method of contraception as outlined in this protocol from at least 14 days before the first dose of study drug and for 90 days following the last dose of study drug.
17. Subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, other staff, or a relative of study personnel directly involved with the conduct of the study.
18. Requirement for more than 1 NSAID after signing informed consent at screening (additional aspirin [second NSAID] <=325 mg/day is allowed). The dose of any ongoing NSAID must be stable for at least 28 days before Day 1.
19. Systemic corticosteroid treatment (prednisone or equivalent) >10 mg/day. The dose of any ongoing systemic corticosteroid must be stable for at least 28 days before Day 1 (Section 16.13).
20. Allergy to gadolinium.
21. Prior treatment with a JAK inhibitor.
22. Other DMARDs (biologic/non-biologic) beyond the required DMARD for study entry must have been discontinued for specified minimum periods before screening (see Section 16.2). Subjects with prior treatment with rituximab/ocrelizumab (or other depleting monoclonal antibody) must show demonstrated recovery of any cytopenia(s).
23. Intraarticular corticosteroids in any joint within 4 weeks before screening, or within 12 weeks before screening for the MRI-designated hand or joint planned for arthroscopy.
24. Treatment with an investigational drug within 60 days or 5 half-lives preceding the first dose of study drug, whichever is longer.
25. Subjects who require concomitant use of any moderate or strong inhibitors or inducers of CYP3A or P-gp or who require CYP3A substrates with serious associated side effects at high exposure (Section 10.3; partial lists in Section 16.3).
26. Have received a live or live attenuated vaccination in the 4 weeks before study Day 1.
27. Positive urine or serum pregnancy test.
28. Hemoglobin <11 g/dL for females or <12 g/dL for males at screening.

29. Absolute neutrophil count <1.5 K/µL at screening.
30. Platelet count <120 K/µL at screening.
31. ALT or AST >=1.5 × the ULN at screening.
32. Creatinine clearance <30 mL/min at screening
33. Positive hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus 1 and 2 antibodies at screening.
34. Other clinically significant out-of-range laboratory results in hematology, serum chemistry, coagulation studies, or urinalysis at the screening as judged by the investigator.

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:	4
Type:	Anticipated

Ethics review

Approved WMO Date:	27-03-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-05-2013
Application type:	First submission

Review commission: METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2012-003439-41-NL
ClinicalTrials.gov	NCT01754935
CCMO	NL42286.041.12