A randomized, double-blind, placebo-controlled, phase 2 study to evaluate the safety and efficacy of CCX354-C in subjects with rheumatoid arthritis partially responsive to methotrexate therapy.

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

Summary

ID

NL-OMON34107

Source
ToetsingOnline

Brief title
CARAT 2

Condition

- Autoimmune disorders

Synonym
RA, rheumatoid arthritis

Research involving

Human

Sponsors and support

Primary sponsor: Chemocentryx
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: efficacy, Rheumatoid Arthritis, safety, tolerability

Outcome measures

Primary outcome

The primary safety endpoint is the subject incidence of adverse events.

The main efficacy endpoints include:

1. Change from baseline to Week 12 in DAS28-CRP.

2. ACR20, ACR50, and ACR70 Response at Week 12.

3. Proportion of subjects achieving a DAS28-CRP score less than 2.6 (remission)

at Week 12.

4. Proportion of subjects achieving a DAS28-CRP score less than 3.2 (low

disease activity) at Week 12.

Secondary outcome

Other safety endpoints include:

1. Subject incidence of serious adverse events

2. Subject incidence of withdrawals due to adverse events

3. Change from baseline in all safety laboratory parameters

4. Change from baseline in vital signs

5. Clinically significant ECG abnormalities.

Other efficacy endpoints include:

1. Proportion of subjects achieving the MCID of 0.22 in HAQ-DI at Week 12.

2. Change from baseline to Week 12 in the components of the DAS28 and ACR, including the swollen joint count, the tender/painful joint count, the subject*s assessment of RA (VAS), the subject*s assessment of pain (VAS), the physician*s assessment of the subject*s RA (VAS), the HAQ-DI, CRP, and ESR.

3. Change from baseline to Week 12 in DAS28-ESR.

4. Change from baseline to Week 12 in duration of morning stiffness.

Study description

Background summary

Rheumatoid arthritis is a disease without a cure, although a variety of treatment options are available. Non-steroidal anti-inflammatory drugs, selective cyclooxygenase 2 (COX-2) inhibitors, and glucocorticoids are useful in reducing pain and suppressing inflammation. However, these compounds are not effective in preventing progression of joint damage and have well-known side effects, such as gastrointestinal bleeding and increased risk of heart attack and stroke. Disease-modifying anti-rheumatic drugs, such as methotrexate, leflunomide, and sulfasalazine, are effective in retarding joint damage. However, long-term use of these drugs has serious side effects that result from immune suppression. Although newer biologic agents such as infliximab, etanercept, anakinra, adalimumab, abatacept, and rituximab have improved efficacy, these drugs also have significant side effects. Additionally, these protein therapeutics are expensive and need to be administered by infusion or injection. These limitations highlight the need for development of new therapies.
CCX354-C is being developed as an orally delivered, disease-modifying therapy for rheumatoid arthritis and potentially for other diseases such as osteoporosis, psoriasis, and psoriatic arthritis. Because CCX354-C blocks the monocyte migration and macrophage infiltration that occurs only during inflammation, it is anticipated that administration of CCX354-C will provide selective treatment of these diseases without compromising general immune surveillance.

Study objective

The primary objective of the study is to evaluate the safety and tolerability of CCX354-C in subjects with rheumatoid arthritis (RA) who had an inadequate response to methotrexate treatment.
The secondary objectives of the study are to evaluate the efficacy of CCX354-C compared to placebo based on:
1. Change from baseline in RA Disease Activity Score 28-C-reactive protein (DAS28-CRP);
2. Proportion of subjects achieving American College of Rheumatology (ACR) 20, 50, and 70 response criteria;
3. Proportion of subjects achieving a DAS28-CRP value less than 2.6 (remission); and
4. Proportion of subjects achieving a DAS28-CRP value less than 3.2 (low disease activity).
For tertiary objectives of the study, please refer to the study protocol.

Study design

This is a randomized, double-blind, placebo-controlled, parallel group study in approximately 150 subjects with RA who have been partially responsive to methotrexate therapy. Three groups of approximately 50 subjects will be randomized (1:1:1) in this study:
* Group 1: Placebo twice daily for 12 weeks
* Group 2: 100 mg CCX354-C twice daily for 12 weeks
* Group 3: 200 mg CCX354-C in the morning and placebo in the evening daily for 12 weeks
Subjects will be stratified based on prior biologic therapy use or not, and based on current systemic glucocorticosteroid use or not, and will then be randomized to one of the three treatment groups.
Subjects will visit the study center for screening procedures and on Study Day 1 and Study Weeks 1, 2, 4, 8, 12, and 16. At these visits, RA disease assessments will be made, and blood samples will be collected for safety, PK, and pharmacodynamic (PD) measurements. Subjects will be terminated from the study at the Study Week 16 follow-up visit.

Intervention

Subjects will take 2 tablets in the morning (study drug or placebo) and 1 tablet in the evening (study drug or placebo).

Study burden and risks

Subjects have to come to the study center 8 times in total, where several activities will be performed, such as: taking blood samples, having an ECG, having an X-ray (for TB testing) and completing questionnaires. No serious or severe side effects have been reported to date. The most common adverse events reported by healthy volunteers who received CCX354-C were headache, flatulence,

sense of hair loss, dizziness, abdominal pain, cold symptoms, diarrhea, eye redness, and sore throat. The following side effects have been reported by subjects with RA: diarrhea, abdominal pain, dry mouth, fever, itching, nausea, swelling of hands and feet, viral symptoms, vomiting and weakness.

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. Male or female subjects, aged 18-75 years inclusive, with functional class I to III RA based on ACR criteria for at least 3 months prior to screening; wheel-chair bound subjects or those with irreversible disease will not be eligible
2. Subjects must have active RA, defined by a minimum of 8 swollen joints and 8 tender/painfull joints (based on 66/68 joint count), at screening
3. Serum C-reactive protein (CRP) above 5 mg/L at screening

4. Must have been on methotrexate (7.5 to 25 mg/week) taken orally, subcutaneously, or intramuscularly for * 16 weeks and on a stable dose for * 8 weeks prior to randomization.
5. If on hydroxychloroquine, must have been on a stable dose for * 16 weeks prior to randomization
6. If taking non-steroidal anti-inflammatory drugs (NSAIDs), must have been on stable doses for * 2 weeks before randomization
7. If taking oral corticosteroids, subjects may not take more than 10 mg/day of prednisone or equivalent, and must have been on a stable dose for * 4 weeks before randomization.
For more inclusion criteria, please refer to protocol.

Exclusion criteria

1. Diagnosed with RA prior to 16 years of age
2. Women who are pregnant, breastfeeding, or have a positive serum pregnancy test at screening
3. History within one year prior to randomization of illicit drug use
4. History of alcohol abuse at any time in the past
5. Have received sulfasalazine, azathioprine, 6-mercaptopurine, mycophenolate mofetil, tetracycline, cyclosporine, gold, tacrolimus, sirolimus, or other disease modifying anti-rheumatic drug (DMARD) within 8 weeks of randomization;
6. Use of infliximab, adalimumab, abatacept, certolizumab, golimumab, or tocilizumab within 8 weeks of randomization
7. Use of leflunomide within 6 months of randomization
8. Use of etanercept or anakinra within 4 weeks of randomization
9. Use of a B-cell depleting agent such as rituximab or ocrelizumab, or cytotoxic agents, such as cyclophosphamide or chlorambucil, within one year of randomization.
For more exclusion criteria, please refer to 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:	Pending
Start date (anticipated):	01-08-2010
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Not available yet
Generic name:	Not available yet

Ethics review

Approved WMO Date:	04-06-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-12-2010
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	EUCTR2010-019964-36-NL
CCMO	NL32360.018.10