A 26-week, phase II, multicenter, randomized, double-blind, placebo-controlled study to assess the response to treatment (ACR50) and to determine a biomarker profile in responders to ACZ885 (anti-interleukin-1beta monoclonal antibody) plus MTX as compared to MTX alone in early rheumatoid arthritis patients.

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To evaluate the efficacy of ACZ885 plus MTX by assessing the response to treatment (ACR50) as compared to MTX alone in early RA patients after 6, 14 and 26 weeks of treatment. The study aims to evaluate the clinical response in this RA subpopulation...

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

Summary

ID

NL-OMON30757

Source
ToetsingOnline

Brief title
CACZ885A2204

Condition

- Autoimmune disorders
- Joint disorders

Synonym
rheumatism, rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Het onderzoek wordt gefinancierd door de opdrachtgever Novartis Pharma B.V.

Intervention

Keyword: ACZ885A, Biomarker profile, Efficacy, Rheumatoid arthritis

Outcome measures

Primary outcome

Primairy efficacy variable: ACR 50 after 6, 14 and 26 weeks of treatment.

Secondary outcome

Safety and tolerability: vital signs, ECG, lab evaluations, adverse events,

co-medication.

Pharmacokinetic data.

Pharmacodynamicdata: ACR 20, 50, 70 and 90, DAS 28, SDAi, bone structure,

stabilization and/or improvement of (MRI, X-ray) bone mineral density of the

hand.

Biomarkers.

Study description

Background summary

The common golden standard treatment for rheumatoid arthritis (RA) are methotrexate and biological products. These therapies all show various side effects and a significant number of patients is not adequately responding to this treatment. This is also true for newer anti-TNF anti-TNF-* therapies and anakinra. So there is a need for a better therapy for these patients.

ACZ885 is a high-affinity fully human monoclonal anti-human IL-1* antibody of the IgG1/k isotype, being developed as a novel disease-modifying agent for the treatment of rheumatoid arthritis (DMARD), as an alternative first line biologic agent to anti-TNF biologics. It binds to human IL-1*, the main isoform of IL-1 that accounts for most of the IL-1 activities in circulation, and functionally neutralizes the bioactivity of this cytokine. In comparison to other biologic agents, such as anakinra, that blocks IL-1* activity, ACZ885 is more potent with a longer duration of action, and thus, is envisioned to overcome the hypothesized basis for the modest anti-rheumatic activity seen in most patients with anakinra.

Study objective

To evaluate the efficacy of ACZ885 plus MTX by assessing the response to treatment (ACR50) as compared to MTX alone in early RA patients after 6, 14 and 26 weeks of treatment. The study aims to evaluate the clinical response in this RA subpopulation and to investigate a biomarker profile allowing to distinguish between treatment responders and non-responders.

Study design

This will be a 26 weeks treatment, Phase II multi-center, randomized, double-blind, double-dummy, placebo-controlled, 2-arm, mechanism-of-action study in early RA patients.

Intervention

During this study patients will be treated with ACZ885 600 mg (IV) or placebo, both combined with methotrexate.

Study burden and risks

Burden: 20 visits maximum. During these visits the following tests will be performed:
Physical examination (3x), examination of the joint structure (12x), drugs- and

alcohol test (2x), MRI of the wrist (2x), TBC test (2x), Hepatitis B, C and HIV test (1x), Pregnancy test (11x), blood and urine collection (19x), administration of study medication i.v. for 2 hours (5x), intake of methotrexaat (10x), measurement of vital signs and body temperature (19x), length (1x), weight (12x), ECG (7x), Questionnaire completion (12x), X-ray of hands and feet (2x), DEXA of the wrist, spine and hip (2x).
Thus far, 81 male or female adult subjects have received ACZ885. The initial conclusions are that ACZ885 appears very well tolerated and there is no data to suggest any potential safety concerns. ACZ885 has been well tolerated. There was no evidence of drug related changes in vital signs, electrocardiogram, and lab values used to assess safety, in all dose groups. There were no serious adverse events which lead to treatment or study discontinuation and antibodies to ACZ885 have not been detected. There was no evidence of drug related changes in vital signs, electrocardiogram, and lab values used to assess safety.

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 and female patients aged 18 to 75 years.
2. Recent definite diagnosis of RA (less than 3 years ago), classified by American Rheumatism Association 1987 revised criteria.
3. Candidate for methotrexate or biologic due to erosive arthritis, with no contraindications to such therapy, including:
o Negative tuberculin skin test reaction at the screening visit or within 2 months prior to the screening visit. Patients who have a positive PPD skin test, but were previously treated with anti-tuberculosis drugs, or are known to have a negative chest X-ray (within the last year) can be included.
o Normal chest X-ray (within the last year).
4. Functional status class I, II or III classified according to the American College of Rheumatology 1991 revised criteria.
5. Active disease at screening and baseline evaluation, defined as at least 6 swollen and 6 painful tender joints of 28 joint count, and at least one of the following: hsCRP > 1.0 mg/dL, and/or ESR > 28 mm/h.
6. At Screening, and Baseline, vital signs (after 3 minutes of resting) should be within the following ranges:
Young subjects:
Oral body temperature between 35.0-37.5 °C
systolic blood pressure, 90-140 mm Hg
diastolic blood pressure, 50-90 mm Hg
pulse rate, 40 - 90 bpm
Elderly subjects (60-75 years of age):
Oral body temperature between 35.0-37.5 °C
systolic blood pressure, 100-160 mm Hg
diastolic blood pressure, 50-100 mm Hg
pulse rate, 50 - 100 bpm;After 3 minutes standing there shall be no more than a 20 mm Hg drop in systolic or 10 mm Hg drop in diastolic blood pressure and increase in heart rate (>20 bpm) associated with clinical manifestation of postural hypotension.
7. Women of child bearing potential may participate if they have a negative pregnancy test at screening and prior to dosing and are willing to practice double-barrier contraception during the study and for at least 3 months following last study drug administration.
Postmenopausal women must have no regular menstrual bleeding for at least 1 year prior to inclusion (plasma FSH level of >40 IU/L).
Surgically sterilized women must have been sterilized at least 6 months prior to screening.
Male patients must be using a double-barrier local contraception for the entire duration of the study, and refrain from fathering a child in the 3 months following last study drug administration.
8. Weight at least 45 kg.
9. Body mass index (BMI) within the range of 18 to 34.
10. Able to communicate well with the investigator, to understand and comply with the requirements of the study. Understand and sign the written informed consent.

11. Oral corticosteroids are permitted as long as patients are on a stable dose (up to 10 mg) for at least 4 weeks prior to randomization.

Exclusion criteria

1. Contraindication for MRI of wrist.
2. Patients with magnetizable metal parts/devices on and in the body that could interfere with the interpretation of the MRI
3. Patients with an unstable active medical condition likely to impair evaluation of safety and biomarker results.
4. Previous treatment with biological therapy or MTX.
5. Limited kidney function.
6. Previous treatment with other DMARDS within 4 weeks of screening.
7. Intra-articular corticosteroids within 4 weeks prior to screening.
8. Participation in any clinical investigation within 4 weeks prior to dosing.
9. Donation or loss of 400 mL or more of blood within 8 weeks prior to first dosing.
10. Significant illness within two weeks prior to dosing.
11. A past medical history of clinically significant ECG abnormalities or a family history of a prolonged QT-interval syndrome.
12. History of autonomic dysfunction.
13. History of clinically significant acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated).
14. History of clinically significant drug allergy or history of atopic allergy. A known hypersensitivity to the study drug or drugs similar to the study drug.
15. History of disease of the blood building system.
16. History of serious or active infections.
17. History of gastric ulcers.
18. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs or which may jeopardize the patient in case of participation in the study. The investigator should be guided by evidence of any of the following:
19. History of immunodeficiency diseases, including a positive HIV test result.
20. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.
21. History of drug or alcohol abuse within the 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations.

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:	Recruitment stopped
Start date (anticipated):	01-07-2007
Enrollment:	7
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	27-04-2007
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

Approved WMO

Date:	23-05-2007
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

Approved WMO Date:	13-06-2007
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	14-06-2007
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	31-03-2008
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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	EUCTR2006-001553-10-NL
CCMO	NL15408.099.07