A randomized, double-blind, placebo-controlled, dose escalation study of the safety, tolerability and pharmacokinetics of AIN457 in rheumatoid arthritis patients with pharmacodynamics assessed in an expanded cohort at the maximum tolerated dose.

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

Summary

ID

NL-OMON29949

Source
ToetsingOnline

Brief title
AIN study

Condition

- Autoimmune disorders
- Joint disorders

Synonym

rheumatism

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: AIN457, dose escalation, methotrexate, rheumatoid arthritis

Outcome measures

Primary outcome

Safety and tolerability: vital signs, ECG, laboratory results, adverse events

and concomitant medications / significant non-drug therapies.

Pharmacokinetic data

Pharmacodynamic data: ACR20, ACR50 and ACR70 responders and DAS score.

After each cohort has completed treatment, the clinical team will review the

safety and pharmacokinetic data available.

Secondary outcome

biomarkers, immunogenicity of IV AIN457, total and free IL 17 in blood,

pharmacogenetic assessments and pharmacogenomic assessments

Study description

Background summary

The current standard therapies for rheumatoid arthritis (RA) have several side effects and significant non- or partial responders, pointing to a continued medical need for better therapies. AIN457 is a fully human monoclonal antibody neutralizing IL-17A.

There is a strong rationale for the use of an anti-IL-17A approach for the treatment of RA. IL-17A has been described as the missing link between effector memory T cell and inflammation in RA. In RA patients, IL-17A is found elevated in serum, synovial fluid and synovium and, ex vivo, it affects inflammation, cartilage and bone destruction. Several animal data confirm the role of IL-17A in inflammation, cartilage, and bone destruction.

Study objective

The objective of this study is to evaluate the safety, tolerability and pharmacokinetics of AIN457 and to compare the efficacy of AIN457 with placebo, in patients with active RA when administered in combination with a stable dose of methotrexate. The secondary objective is to explore the relationship of potential biological and pharmacogenomic markers of AIN457 activity with clinical efficacy outcomes by assessing the preliminary biologic activity/pharmacodynamics of AIN457.

Study design

This is a three-part, multi-center, randomized, double-blind, placebo-controlled Phase I study. Part I is a single dose escalation study up to 10 mg/kg or the maximum tolerated dose (MTD). Part II is a multiple (2) dose escalation study with dose levels up to 10 mg/kg or the MTD. In part III an expanded cohort will receive 2 doses of 10 mg/kg or the MTD. For each patient the study consists of a screening period, a baseline evaluation and a single treatment period (with one or two doses of study medication) followed by an observation period of 13 * 16 weeks.

Intervention

Patients will receive AIN457 or placebo. Depending on the moment of inclusion the patients will receive in part I: single dose 0.3 mg/kg - 10 mg/kg or MTD, in part II: 2 doses 1.0 mg/kg - 10 mg/kg or MTD and in part III: 2 doses of 10 mg/kg or MTD.

Study burden and risks

Burden: maximal 18 visits. During the visits the following examinations are done: synovial biopsy 0-2 x, admission of study medication i.v. during 2 hours 1-2 x, collection of blood samples maximal 30 x, physical examination 11 x, examination of the joints 15 x, chest X-ray 1 x , ECG 4 - 6 x, hepatitis B and C test, HIV, drugs and alcohol test, tuberculosis test 1 x, pregnancy test 3 of 4 x, influenza and pneumococcal vaccination 1 x, urine collection 16 x, blood pressure, hart rate 17 -24 x, body temperature 17-24 x, questionnaires 10 x, length 1 x, weight 7 x .
Risks: Based on the role of IL-17 in the pro-inflammatory cytokine network in

rheumatoid arthritis, we presume that the safety profile of AIN457 will be comparable to that of biological drugs targeting TNF* and IL-1. Yet there is no direct information on the safety of neutralizing IL-17 in humans. To protect the safety of the patients as good as possible there is a Data Safety Monitoring Board (DSMB) in this study.

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 18-75 years.
2. Diagnosis of active rheumatoid arthritis of stages I, II or III. Disease duration of at least 6 months prior to randomization.
3. (Relatively stable) active disease at screening and baseline evaluation: * 6 tender and * 6 swollen joints of 28 examined and either a) ESR * 28 mm/hour, or b) CRP * 1.5 mg/L. Part 1 of

the study at the 0.3 mg/kg and 1 mg/kg may enroll patients with * 3 tender and/or swollen joints, with no requirements for ESR and CRP since there will be no efficacy measurements done at those dose levels.
4. Patients must be on a current treatment with methotrexate * 25 mg/week and with the current dose stable for at least 3 months. Prior treatment with 1*3 DMARDs. Patients should have failed at least 1 DMARD including methotrexate.
5. Patients with a total white cell count, platelet count, hemoglobin and hematocrit values that are clinically acceptable for patients with RA
6. Patients with a history of immunization for Influenza (within past 12 months) and Pneumococcal vaccination (within 4 years).

Exclusion criteria

1. Current treatment with anti-TNF-* or anti IL-1 therapy (or other biological therapy), or immunosuppressive agents.
2. If patient has been discontinued from other DMARDs for lack of efficacy or toxicity, the patient should be at least 1 month off the agent and the effects of that agent should have dissipated according to the recognized duration of effect, or standard washout procedure. Importantly, discontinuation should not be undertaken only for the purposes of participation in this study.
3. Patients with congestive heart failure (NYHA > III) or poorly controlled diabetes mellitus (HbA1c value * 10%).
4. Patients who have received intra-articular or systemic corticosteroid injections for treatment of acute RA flare within four weeks prior to randomization OR who require strong narcotic analgesics that can mask the pain symptoms required as an entry criterion.
5. Presence of major chronic inflammatory autoimmune diseases that can mimic rheumatoid arthritis diagnosis or that can interfere with efficacy evaluation in the study.
6. History of renal trauma, glomerulonephritis or patient with one kidney.
7. Treatment with an investigational agent within 12 weeks prior to enrollment.
8. Presence of severe physical incapacity (Steinbrocker Class IV)
9. Pregnant or breastfeeding women.
10. Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing
11. A positive HIV, hepatitis B, hepatitis C or tuberculin test result.
12. Significant illness within the two weeks prior to dosing or any active systemic infection or medical condition that may require treatment or therapeutic intervention during the study.
13. History of severe hypersensitivity to any biological agents, a history of serious allergic reaction, collagen disease, neurological disease.
14. History of any joint surgery in past 8 weeks or planned surgery within next 5 months.
15. History of malignancy.
16. History or evidence of drug or alcohol abuse within the 6 months prior to dosing.
17. Presence of clinically significant proteinuria, creatinine, active sediments, casts or WBCs in urine.
18. Presence or history of underlying metabolic, endocrine, hematologic, pulmonary, cardiac, blood, renal, hepatic, infectious, psychiatric or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at

unacceptable risk for participation in a study of an immunomodulatory therapy.

Study design

Design

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):	01-09-2006
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Niet geregistreerd geneesmiddel
Generic name:	Niet geregistreerd geneesmiddel

Ethics review

Approved WMO Date:	10-07-2006
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2006
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-01-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2007
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	EUCTR2006-000375-15-NL
CCMO	NL12050.018.06