A single dose clinical trial to study the safety of ART-I02 in patients with rheumatoid arthritis

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Primary objectiveTo evaluate the safety and tolerability of a single intra-articular administration of ART-I02, a recombinant adeno-associated virus (AAV) type 2/5 vector in subjects with RA and active arthritis in the wrist.Secondary objectives1....

Ethical review	Not approved
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON43315

Source
ToetsingOnline

Brief title
ART-I02 in patients with RA

Condition

- Autoimmune disorders

Synonym
rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Arthrogen B.V.
Source(s) of monetary or material Support: Arthrogen

Intervention

Keyword: AAV, gene therapy, intra-articular, rheumatoid arthritis

Outcome measures

Primary outcome

The primary endpoints are safety and tolerability, as assessed by

1. treatment emergent (serious) adverse events

2. concomitant medication

3. clinical laboratory tests

a. haematology

b. chemistry

c. urinalysis

4. vital signs

a. pulse rate

b. systolic blood pressure

c. diastolic blood pressure

d. body temperature

5. ECG parameters

a. HR, PR, QRS, QT and Qtc

Secondary outcome

The following secondary endpoints are (functional) assessments to evaluate the

safety and tolerability of the ART-I02 injection:

1. Change from baseline after single dose of ART-I02 for clinical signs and

symptoms of the target joint evaluated by the CCI and its individual components

over 24 weeks.

2. Change from baseline after single dose of ART-I02 on hand function measured by the Cochin Hand Function Scale Questionnaire and a Grip strength measurement, VAS pain (in target and contralateral joint), VAS function (target and contralateral joint), over 24 weeks.

3. Change from baseline on synovitis and osteitis in the injected joint (target joint) evaluated by Magnetic Resonance Imaging (MRI) 12 and 24 weeks after administration of ART-I02 using the OMERACT RA MRI score (RAMRIS).

4. Shedding of ART-I02: evaluation of whole peripheral blood, urine, faeces and saliva analysis for the presence of ART-I02 vector DNA.

5. Induction of immune responses against AAV5 and hIFN-* after a single dose of ART-I02.

Study description

Background summary

The safety and tolerability of the concept of locally introducing a recombinant adeno-associated viral vector (rAAV) expressing the anti-inflammatory IFN-* under the influence of a promoter, which is induced by an inflammatory stimulus will be tested in a relevant disease model. The disease model selected to test the concept is the inflamed joint in patients with rheumatoid arthritis.

Despite the increasing number of treatment options, a subset of patients with RA relapses and has active disease with one or more joints still displaying persistent signs of inflammation while the inflammation of other joints has been greatly reduced. This means that for the joint(s) still affected by active inflammation other therapies are required.

Therefore, there is a need for additional RA therapies with good tolerability and efficacy profiles that can be used in patients who suffer from a few inflamed joints despite previous treatment. Intra-articular gene therapy could provide a solution by providing local treatment for arthritis, with prolonged expression of a therapeutic protein at the site of inflammation after a single

injection.

Study objective

Primary objective
To evaluate the safety and tolerability of a single intra-articular administration of ART-I02, a recombinant adeno-associated virus (AAV) type 2/5 vector in subjects with RA and active arthritis in the wrist.

Secondary objectives
1. To explore the response to a single intra-articular dose of ART-I02 by assessing clinical signs and symptoms of the target joint using the Composite Change Index (CCI) as well as the individual components of the index.
2. To explore the response to a single intra-articular dose of ART-I02 by assessing hand function using the Cochin Hand Function Scale Questionnaire and a Grip strength measurement.
3. To explore the response to a single intra-articular dose of ART-I02 by evaluating synovitis and osteitis in the injected joint by Magnetic Resonance Imaging (MRI).
4. To evaluate shedding of ART-I02 after a single intra-articular dose of ART-I02.
5. To explore the effect of a single intra-articular dose of ART-I02 on inflammation markers in synovium biopsies.
6. To assess immune responses against adeno-associated virus serotype 5 (AAV5) and human interferon beta (hIFN-*) after a single intra-articular dose of ART-I02.

Study design

This is a phase I open label, dose escalating study to investigate the safety of a single intra-articular ART-I02 injection in patients with RA and active arthritis of a wrist. The duration of the study is estimated to be one year, but is depending on the patient recruitment rate. Study duration for each individual patient will be approximately 27 weeks. Patients will be followed for 24 weeks after single intra-articular injection of ART-I02. After this period patients will be rolled over in a long term follow-up study until 5 years after the ART-I02 injection, to assess long term safety.

Long-term follow-up after dosing will consist of annual contact by telephone, performed by the investigator or designee, and will consist of a semi-structured interview designed to solicit information about hospitalizations and new medical conditions, focusing on the development of new and recurrent cancer, development of infection and neurologic, hematologic and autoimmune disorders (other than RA).

Intervention

Single intra-articular administration of ART-I02

Study burden and risks

During this study the patients are at risk of side effects which are known in the use of IFN-beta. The most common side effect is local reaction at the site of the injection. A complication that may occur as a result of the procedures are minimal.

During the study, the patients will visit the research centre a total of 11 times and 5 yearly follow up controls by phone. The patient will undergo examinations and completing questionnaires during the hospital visits.

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

Eligible subjects must meet all of the following inclusion criteria at screening:;1. Female subjects (age *18 years) must be post-menopausal for at least one year (defined as amenorrhea * 12 consecutive months without another cause, and confirmed by follicle stimulating hormone level > 35 mIU/mL)
2. Patient has been diagnosed with RA according to the 2010 American College of Rheumatology/ European league against rheumatism (ACR/EULAR) criteria for the classification of RA, outlined in appendix A.
3. Inflammation of the target wrist due to active RA as confirmed by MRI.
4. Written informed consent, able and willing to comply with the requirements of the study protocol.
5. Judged to be in general good health with, in the opinion of the investigator, no other clinically significant and relevant abnormalities of medical history, and no abnormalities at the physical examination, vital signs, electrocardiography (ECG) and laboratory safety tests, performed at the screening visit and/or prior to administration of ART-I02.

Exclusion criteria

Eligible subjects must meet none of the following exclusion criteria at screening:;1. Arthrodesis or joint replacement of the target wrist prior to inclusion.
2. Known hypersensitivity to natural or recombinant hIFN-*, or to any excipients.
3. Contra-indication for intra-articular treatment.
4. Presence of neutralizing antibody (Nab) titers against adeno-associated virus type 5 (AAV5) and/or hIFN-*.
5. Active infectious disease of any nature, including clinical active viral infections.
6. Previous treatment with an AAV 5 vector.
7. Oral corticosteroid therapy at doses higher than the equivalent of 10 mg prednisone per day within 4 weeks prior to administration of the study medication.
8. Intra-articular or parenteral corticosteroid treatment within one month prior to the administration of the study medication.
9. Current use of a Tumor Necrosis Factor alpha antagonist (TNF-* antagonist), (including etanercept, certolizumab, adalimumab, infliximab, golimumab) or anakinra, and other biological agents including abatacept, tocilizumab and rituximab.
10. Poor functional status, defined as being bed-bound or wheelchair-bound.
11. Participation in an investigational drug or device study within 90 days prior to screening or more than 4 times per year.
12. Positive for human immunodeficiency virus (HIV) infection, hepatitis C antibodies or hepatitis B surface antigen.
13. Positive for anti-double-stranded DNA antibodies (dsDNA).
14. History of liver function abnormality requiring treatment, drug induced liver injury, chronic liver disease, excessive alcohol consumption or chronic alcohol induced disease.
15. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x upper limit of normal (ULN), or bilirubin 2 x ULN. If a subject has AST or ALT > 2 x ULN but < 2.5 x ULN, re-

assessment is allowed at the investigator*s discretion.
16. Severely impaired renal function (estimated glomerular filtration rate * 30 mL/min according to the Cockcroft-Gault formula).
17. Subject had a major surgery, donated or lost approximately 500 mL blood within 4 months prior to the screening visit
18. Mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude
19. Serious medical disease, such as severe liver or kidney disease, uncompensated congestive heart failure, myocardial infarction within six months, unstable angina, uncontrolled hypertension, severe pulmonary disease or active asthma, demyelinating neurological disease, depression or a history of depression, history of seizures or epilepsy, uncontrolled epilepsy, or history of cancer (other than cutaneous basal and squamous cell carcinoma or cervical intraepithelial neoplasia) with less than five years documentation of a disease-free state, recurrent opportunistic infections or other concurrent medical condition that, in the opinion of the investigator, would make the subject unsuitable for the study.
20. Investigator has concerns regarding the safe participation of the subject in the trial or for any other reasons: the investigator considers the subject inappropriate for participation in the trial.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

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

Ethics review

Approved WMO

Date:	07-04-2016

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	27-07-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2013-004763-31-NL
ClinicalTrials.gov	NCT02727764
CCMO	NL56708.000.16