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

Published: 29-11-2016
Last updated: 11-04-2024

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 expressing human IFN-β in patients with RA or OA and active arthritis...

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

Summary

ID

NL-OMON45686

Source
ToetsingOnline

Brief title
ART-I02 in patients with Arthritis

Condition

- Autoimmune disorders

Synonym
arthritis

Research involving
Human

Sponsors and support

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

Intervention

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

Outcome measures

Primary outcome

Safety and tolerability endpoints

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. and ECG parameters

a. HR, PR, QRS, QT and Qtc

Secondary outcome

Secondary endpoints

The secondary endpoints are safety and tolerability as assessed by:

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 CMC, MCP, PIP, DIP extension/ flexion over 24 weeks.

3. Change from baseline after single dose of ART-I02 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.

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

5. Induction of humoral and cellular immune responses against AAV5 and hIFN-β after a single dose of ART-I02 by measuring antibodies against AAV5 and IFN-β, neutralizing antibodies to AAV5 and hIFN-β, and T cell responses against AAV5 and hIFN-β, respectively.

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-β 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 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.
For OA few treatment options are available, and those that are available, consist of mitigation of pain rather than preventing progression of disease.

Therefore, there is a need for additional 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 expressing human IFN-β in patients with RA or OA and active arthritis of the carpometacarpal (CMC), metacarpophalangeal (MCP), proximal interphalangeal (PIP), or distal interphalangeal (DIP) joints with an indication for a surgical intervention of the target joint.

Secondary safety and tolerability objectives are:
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 CMC, MCP, PIP or DIP range of motion.
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 assess immune responses against adeno-associated virus serotype 5 (AAV5) and human interferon beta (hIFN-β) after a single intra-articular dose of ART-I02.

Study design

This is a phase I, open label, monocenter, dose escalation study evaluating the safety of single intra-articular administration of ART-I02 in 12 rheumatoid arthritis (RA) and OA patients with active arthritis of the CMC, MCP, PIP and/or DIP joint with an indication for a surgical intervention of the target joint. The study will be performed at the Centre for Human Drug Research (CHDR). Patients will be screened maximally 3 weeks prior to administration of ART-I02 and will be evaluated for at maximum 24 weeks post administration before they continue in a Long Term Follow Up study until 5 years after the ART-I02 injection.

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 center 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

Public
Arthrogen B.V.

Meibergdreef 45
Amsterdam 1105 BA
NL
Scientific
Arthrogen B.V.

Meibergdreef 45
Amsterdam 1105 BA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients >=18 years of age
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 B or OA as confirmed by their treating physician/specialist.
3. Patient is scheduled for surgical intervention of the target joint.
4. Inflammation of the CMC, MCP, PIP or DIP joint as confirmed by MRI.
5. Written informed consent, able and willing to comply with the requirements of the study protocol.
6. 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.
7. Females are not pregnant nor lactating. All patients use effective contraception in combination with barrier contraception for the first three months after administration or until three consecutive semen samples are negative.

Exclusion criteria

1. Arthrodesis or joint replacement of the CMC, MCP, PIP or DIP joint prior to inclusion.
2. Known hypersensitivity to natural or recombinant hIFN-β, or to any excipients.
3. Contra-indication for intra-articular treatment.
4. Presence of neutralising antibody (Nab) titers against adeno-associated virus type 5 (AAV5) and/or hIFN-β.
5. Active infectious disease of any nature, including clinical active viral infections.
6. Previous treatment with an AAV 5 vector.
7. Poor functional status, defined as being bed-bound.
8. Participation in an investigational drug or device study within 90 days prior to screening or more than 4 times per year.
9. Positive for human immunodeficiency virus (HIV) infection, hepatitis C antibodies or hepatitis B surface antigen.
10. Positive for anti-double-stranded DNA antibodies (dsDNA).
11. History of liver function abnormality requiring treatment, drug induced liver injury, chronic liver disease, excessive alcohol consumption or chronic alcohol induced disease.
12. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x upper limit of normal (ULN), or bilirubin > 2 x ULN. If a patient has AST or ALT > 2 x ULN but < 2.5 x ULN, re-assessment is allowed at the investigator*s discretion.
13. Severely impaired renal function (estimated glomerular filtration rate <= 30 mL/min according to the Cockcroft-Gault formula).
14. Patient had a major surgery, donated or lost approximately 500 ml blood within 4 months prior to the screening visit
15. Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude
16. 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 patient unsuitable for the study.
17. Investigator has concerns regarding the safe participation of the patient in the trial or for any other reasons: the investigator considers the patient 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:	Recruitment stopped
Start date (anticipated):	24-04-2018
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO

Date:	29-11-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	14-02-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	06-09-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-12-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-02-2018
Application type:	Amendment
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	EUCTR2016-004609-15-NL
ClinicalTrials.gov	NCT02727764
CCMO	NL59913.000.16