A PHASE 3 DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF AMG0001 IN SUBJECTS WITH CRITICAL LIMB ISCHEMIA

Published: 27-11-2014
Last updated: 22-04-2024

The primary objectives of the clinical trial are:1. To estimate the treatment benefit (AMG0001 compared to placebo), in terms of a combined endpoint (major amputations or all-cause death)2. To evaluate the overall safety and efficacy of AMG0001.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON42192

Source
ToetsingOnline

Brief title
AnGes AG-CLI-0206

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Critical limb ischemia

Research involving
Human

Sponsors and support

Primary sponsor: AnGes Inc.
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: AG-CLI-0206, AMG0001, Critical limb ischemia, Phase 3

Outcome measures

Primary outcome

Time to major amputation of the index leg (at or above the ankle) or all-cause

death.

Secondary outcome

Percentage of subject who have undergone major amputation or revascularization

of the index leg

Time to complete ulcer healing of the largest baseline ulcer on the index leg

up to 18 months (ulcer should remain healed for at least 2 weeks)

Ischemic rest pain reduction of the index leg using a 10 cm VAS scale in

Rutherford 4 and 5 subjects over 18 months

Changes in the quality of life (using EuroQol (EQ-5D-5L) and VascuQol) over 18

months

Time to major amputation (of the index leg) or CLI-related deaths up to 18

months

CLI- related deaths include but are not limited to: deaths due to complications of CLI (e.g., septicemia), peri-operative deaths occurring within one month of bypass surgery or major amputation. Deaths will be adjudicated by at Adjudication Committee in a blinded manner.

Incidence of Stroke and Myocardial Infarction up to 18 months

Primary bypass graft patency for those subjects that receive open surgical bypass at 18 months

Study description

Background summary

Peripheral artery disease (PAD) affecting the lower limbs results from the consequences of atherosclerosis. Critical limb ischemia (CLI) is the severest form of PAD and occurs when tissue viability is jeopardized at rest. The chief manifestations of CLI include ischemic pain at rest (Rutherford class 4, Fontaine class 3) and/or tissue loss (Fontaine class 4 or Rutherford class 5 when tissue loss is minor and Rutherford class 6 when tissue loss is major) resulting in ischemic ulceration and gangrene.

The management of CLI includes risk factor modification including the treatment of hyperlipidemia, hypertension, diabetes, and smoking. In addition, analgesics (often opioids) are used for the relief of rest pain. Meticulous foot care and local wound care are important to prevent or manage tissue loss. Finally the majority of patients are treated with antiplatelet therapy and a statin. The current management, in addition to the above, includes revascularization by surgery or by endovascular interventions. Up to 15% of subjects are unsuitable for either of these forms of revascularization procedures while others (~40%) are at high risk (poor candidates) for surgical revascularization. Even though revascularization procedures have improved survival and may delay the need for major amputation (amputation at or above the ankle), their effectiveness is often short-lived and surgery is associated with significant morbidity.

Subjects unsuitable for revascularization are candidates for major amputation.

This procedure is associated with considerable morbidity, a poor quality of life, and complications including, in some cases, death.

Subjects with CLI have, overall, a poor prognosis with a 5-year mortality of 50%. Their quality of life is comparable to the quality of life of subjects with advanced cancer. No systemic drug treatment is available for the treatment of CLI. There is an urgent medical need for additional management options.

One such option that is being investigated is *therapeutic angiogenesis.* Therapeutic angiogenesis involves the use of angiogenic growth factors or stem cells to grow blood vessels, improve blood flow, and increase tissue perfusion in the ischemic area. Clinically, the benefit should include the relief of rest pain, the healing of ischemic ulcers and a reduction in the incidence of major amputations.

Study objective

The primary objectives of the clinical trial are:
1. To estimate the treatment benefit (AMG0001 compared to placebo), in terms of a combined endpoint (major amputations or all-cause death)
2. To evaluate the overall safety and efficacy of AMG0001.

Study design

This is a double-blind, randomized, placebo-controlled, phase 3, multinational, multicenter (up to 100 centers) study of AMG0001 (HGF plasmid) in subjects with CLI. The study is event driven (243 primary endpoint events) and 500 CLI subjects are targeted for enrollment. Subjects eligible for the study are CLI subjects (due to atherosclerotic arterial disease of the lower limb) with no option for revascularization by surgical bypass or endovascular intervention, or have a poor option (high risk) for revascularization by surgical bypass but no option for an endovascular intervention (Type D lesions or worse using the TASC II classification). Clinic visits will occur for screening, Days 0, 14, 28, 42, Month 3, Month 3+14 days, Month 3+28 days, Month 3+42 days, Month 6, Month 9, Month 9+ 14 days, Month 9 + 28 days, Month 9 +42 days, Month 12, Month 12+14 days, Month 12+28 days, Month 12+42 days, Month 15, and Month 18. Post-18 month follow-up data for the primary efficacy events and revascularization of the index limb will be obtained using a questionnaire every 3 months until the last subject enrolled completes the 18 Month Visit. Post-18 month safety follow-up data will be obtained for all subjects using a questionnaire every 3 months for a minimum 1.5 years after the 18 Month Visit. The total duration of the study will be 18 months by clinic visits and up to ~ 24 months by questionnaire.

Intervention

The study product will be administered by eight (8) intramuscular injections delivered to the index leg (see Inclusion Criteria for definition of index leg) at each dosing visit (see table below). For each of the 8 injections, 3 mL of AMG0001 or matching placebo will be injected in about 3 seconds.

First Cycle
Day 0, Day 14, Day 28, and Day 42
(4 sets of injections, 2 weeks apart; each set is 4 mg subdivided into 8 injections of 0.5 mg of HGF plasmid in 3 mL saline or matching placebo)
Month 3, Month 3+14 days, Month 3+28 days, and Month 3+42 days
(4 sets of injections, 2 weeks apart; each set is 4 mg subdivided into 8 injections of 0.5 mg of HGF plasmid in 3 mL saline or matching placebo)

Second Cycle
Month 9, Month 9+14 days, Month 9+28 days, and Month 9+42days
(4 sets of injections, 2 weeks apart; each set is 4 mg subdivided into 8 injections of 0.5 mg of HGF plasmid in 3 mL saline or matching placebo)
Month 12, Month 12+14 days, Month 12+28 days, and Month 12+42 days
(4 sets of injections, 2 weeks apart; each set is 4 mg subdivided into 8 injections of 0.5 mg of HGF plasmid in 3 mL saline or matching placebo)

Study burden and risks

This research study consists of injecting DNA (HGF Plasmid) into the leg muscle so that cells in the tissue will produce Hepatocyte Growth Factor protein and hopefully cause new blood vessels to grow from existing blood vessels. Although there is currently no evidence to suggest that DNA transferred to the muscle in this fashion is harmful, there is a possibility that abnormal events could occur within normal cells that take up this DNA. However, because this is a new and experimental agent, it is not known whether cells could become abnormal after a long period of time and long term studies in humans have not been done. This study will help by evaluating the safety of subjects receiving HGF plasmid for 3 or more years.

There is a possibility that the Hepatocyte Growth Factor that the body produces from the injections of HGF Plasmid could increase the growth of an existing tumor in the body.

There is a chance that HGF Plasmid may worsen already bad eyesight due to abnormal growth of blood vessels in the retina. In smaller studies undertaken thus far, worsening blood vessel growth in the retina has not been seen.

Some early studies with other types of gene transfer agents have suggested the possibility of permanent genetic alterations in sperm (men) or eggs (women). These changes could have no effect or may eventually cause abnormalities. Some of these changes could lead to miscarriage or abnormalities in future generations. The likelihood of such outcomes is currently unknown. While these

effects have not been seen with animal studies of HGF Plasmid, and it is not an expected side effect since HGF Plasmid does not become a permanent part of the genetic material, conclusive information regarding such effects in animal and human studies is not yet available.

It is not known whether HGF Plasmid can cause harm to pregnant women, fetuses, and newborn children, or if it can affect reproductive capacity of sperm (men) or egg (women). Because of the uncertain risk of transmission of HGF Plasmid through intimate contact, male subjects of reproductive potential must agree to use an accepted and effective (barrier) form of birth control starting with the first dose of study product and continue for 12 weeks from the last dose of study product. Women of child bearing potential will not be allowed to enroll in this study.

Human studies in patients with Critical Limb Ischemia have shown mild to moderate discomfort at the injection sites, which is short-lived. Injection site discomfort has included transient pain, bruising and swelling in the area of the injections. Most side effects that were reported in human trials were due to worsening symptoms and signs of Critical Limb Ischemia or due to other illnesses that are prevalent in older patients (such as strokes, heart attacks, chronic bronchitis or pneumonia). No specific laboratory test abnormalities due to HGF Plasmid have been reported.

Contacts

Public
AnGes Inc.

Motor City Drive, Suite 430 10411
Bethesda MD 20817
US
Scientific
AnGes Inc.

Motor City Drive, Suite 430 10411
Bethesda MD 20817
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subjects with CLI (Severe Rutherford 4 and Rutherford5) who have:
* No option for revascularization by endovascular intervention or surgical bypass OR
* Poor option (high risk) for revascularization by surgery and no option for an endovascular intervention (see Section 3.1 Study Population for full definition for appropriate inclusions).
2. Subjects 40-90 years of either gender who have signed an informed consent form either directly or through a legally authorized representative.
3. Subjects currently are taking a statin and an anti-platelet agent (e.g., clopidogrel, ticlopidine, aspirin, etc.) for 2 weeks or more prior to Day 0 as part of their standard of care, unless contraindicated. Subjects for whom these agents are contraindicated will have the reason for contraindication recorded in their case report form (CRF).
4. If female, the subjects must not be of child bearing potential, e.g., post-menopausal or surgically sterile.
5. If a male subject is of reproductive potential, he must agree to use an accepted and effective (barrier) form of birth control starting with the first dose of study product and continue for 12 weeks from the last dose of study product. This applies to both courses of treatment.
6. Subjects with a previous medical history of myocardial infarction and/or stroke should have adequate management of risk factors to prevent secondary occurrence.
7. Subjects should have the ability to understand the requirements of the protocol and agree to return for the required study visits, assessments and follow up.

Exclusion criteria

1. Subjects whose CLI status is unstable (spontaneous marked improvement or marked worsening during the screening period) or who have excessive tissue necrosis that is unlikely to benefit from medication, or those poor option subjects requiring immediate revascularization by surgery. Stability of the CLI status will be confirmed by the Principal Investigator prior to randomization and retrospectively reviewed by the Adjudication Committee.
2. Subjects who may require a major amputation (amputation at or above the ankle) within 4 weeks of Day 0 (± 4 weeks of Day 0).

3. Subjects with ulcers with exposure of tendons, osteomyelitis or uncontrolled infection or with the largest ulcer that is greater than 20 cm2 in area (>10 cm2 area if on the heel).
4. Subjects with purely neuropathic, or with venous ulcers.
5. Subjects in Rutherford 6 class.
6. Subjects who have had revascularization by surgery or angioplasty within 3 months, unless the procedure has failed based on the anatomy or the hemodynamic measurements.
7. Subjects with a diagnosis of Buerger*s disease (Thrombo-angiitis Obliterans).
8. Subjects currently receiving immunosuppressive, chemo or radiation therapy.
9. Evidence or history of malignant neoplasm (clinical, laboratory or imaging) except for successfully excised basal cell or squamous cell carcinoma, or successfully excised early melanoma of the skin. Subjects, who had successful tumor resection or radio-chemotherapy of breast cancer more than 10 years prior to inclusion in the study, and with no recurrence, may be enrolled in the study. Subjects, who had successful tumor resection or radio-chemotherapy of all other tumor types and have been in remission for more than 5 years prior to inclusion in the study, and with no recurrence, may be enrolled in the study. A dermatological exam will have ruled out any skin cancer.
10. Subjects who have proliferative retinopathy, or moderate or severe non-proliferative retinopathy, from any cause (ETDRS Score > 35), clinically significant macular oedema or previous panretinal photocoagulation therapy (Results from the Early Treatment Diabetic Retinopathy Study. Ophthalmology May 1991 Supplement 98: 823-833).
11. Females of child-bearing potential defined as subjects that are not surgically sterile or post-menopausal.
12. Subjects with severe renal disease defined as significant renal dysfunction evidenced by an estimated creatinine clearance of <30 mL/minute (calculated using the Cockroft Gault formula), or receiving chronic hemodialysis therapy.
13. Any co-morbid condition likely to interfere with assessment of safety or efficacy endpoints, acute cardiovascular events (i.e., CVA, MI, etc.) within 3 months of treatment, or any disease that in the opinion of the Investigator may result in subject mortality in less than 3 months.
14. Subjects with known liver disease (e.g., hepatitis B or C or cirrhosis of the liver).
15. A subject with HIV, AIDS, severe uncontrolled inflammatory disease or severe uncontrolled autoimmune disease (e.g., ulcerative colitis, Crohn*s disease, etc).
16. Subjects who have a significant psychiatric disorder or mental disability that could interfere with the subject*s ability to provide informed consent or comply with study procedures.
17. Subjects with a current, uncorrected history of alcohol or substance abuse.
18. Diabetic subjects with an uncorrected HbA1c > 9.0% during the screening period.
19. Subjects that have been administered rhPDGF (e.g, becaplermin) or other growth factors locally within one month of randomization.
20. Subjects who have received another investigational drug within 30 days of randomization or have previously received any gene transfer therapy within 3 years of entering the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO Date:	27-11-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-05-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-07-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-08-2015
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-10-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-01-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-03-2016
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	EUCTR2014-001129-34-NL
ClinicalTrials.gov	NCT02144610
CCMO	NL50047.000.14