A randomized double blind placebo controlled ascending dose study to evaluate the effect of APL180 on endothelial function in patients with familial hypercholesterolemia

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Assess whether APL180 can improve endothelial function in patients with Familial hypercholesterolemia

Ethical review	Approved WMO
Status	Pending
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON32563

Source
ToetsingOnline

Brief title
APL180

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
atherosclerosis, familial hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis;farmaceutische industrie

Intervention

Keyword: apoAI mimetic peptide, endothelial function, familial hypercholesterolemia, plethysmography

Outcome measures

Primary outcome

change in endothelial function, assessed as acetylcholine-induced vasodilation

in the forearm

Secondary outcome

1. side effects

2. APL180 concentration

3. in vitro HDL quality

Study description

Background summary

Novel strategies are required to further reduce cardiovascular disease burden.

Endothelial dysfunction is an important risk factor for cardiovascular disease. Patients with increased LDL, of which familial hypercholesterolemia is a typical example, are characterized by extreme endothelial dysfunction. As such, restoration of endothelial dysfunction is a widely accepted therapeutic target in these patients.

HDL cholesterol usually protects against vascular disease. This not only relates to its impact on reverse cholesterol transport but also to a direct beneficial effect of its most abundant structural protein, apoAI. ApoAI protects the vessel wall and exerts a whole array of other beneficial effects. Recently, it has become clear that the protective effect of HDL may deteriorate in certain groups of patients, amongst which patients with FH. This is termed

dysfunctional HDL
In experimental models APL-180 has been shown to be able to restore the protective capacity of HDL in these patients, which is accompanied by improvement of endothelial function.

Study objective

Assess whether APL180 can improve endothelial function in patients with Familial hypercholesterolemia

Study design

randomized, double blind, placebo controlled, dose escalation study

Intervention

APL180 or placebo infusion
APL 180 will be administered in 2 dosages: 1 mg/hour and 6 mg/hour (see page 22 protocol)

Study burden and risks

Patients will visit the AMC for 3 separate visits, in total 14 hours.
During one of these visits, a forearm plethysmography will be performed.
The burden of this may pertain to:
- inflating a pulse cuff (160 mmHg, max 5 mintues in a row)
- insertion of 2 venous catheters
- insertion of 1 arterial catheter

Adminstered substances:
- for the forearm studies acetylcholine, nitroprusside and vitamin C will be administered. These are well known, well characterized substances with a short half life. Since these substances will be administered locally, the concentrations systemically will be extremely low. If any side effects were to occur, this may include: bradycardia, hypotension, flushing, sweating. Of note, all patients will be continuously monitored (ECG monitoring, blood pressure registration)

- APL 180: up to now, APL180 was tolerated very well. APL180 is a 22-aminoacid peptide, which is identical to a small part of the endogenous apoAI (structural protein of HDL cholesterol). Potential side effects include: hypoglycaemia, sinsitis, backpain. Side effects always were mild and transient (see protocol page 19).

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

Familial hypercholesterolemia
age 18-50 yrs
informed consent
BMI 18-30 kg/m2

Exclusion criteria

smoking
previous cardiovascular event
diabetes
acute inflammatory disease

anti-inflammatory medication
ECG abnormalities

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:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	29-07-2008
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	APL180
Generic name:	APL180

Ethics review

Approved WMO

Date:	06-08-2008
Application type:	First submission
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	EUCTR2008-002848-41-NL
CCMO	NL24315.018.08