A placebo-controlled, double-blind, randomized trial to compare the effect of different doses of ALN-PCSSC given as single or multiple subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C.

Published: 17-11-2015
Last updated: 19-04-2024

PRIMARY OBJECTIVE The primary objective of this study is to evaluate the effect of ALN-PCSSC treatment on LDL-C levels at Day 180. SECONDARY OBJECTIVESThe secondary objectives of this study are to evaluate the effect of ALN-PCSSC on the following...

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

Summary

ID

NL-OMON43890

Source
ToetsingOnline

Brief title
A study to evaluate the effect of ALN-PCSSC treatment on LDL C levels.

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Atherosclerosis

Research involving

Human

Sponsors and support

Primary sponsor: Medicines Company
Source(s) of monetary or material Support: The Medicines Company (Industry)

Intervention

Keyword: Atherosclerosis, Placebo-controlled, Randomized

Outcome measures

Primary outcome

Parameters to be assessed will include: total cholesterol (TC), triglycerides,

LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very

low-density lipoprotein (VLDL), apolipoprotein A1 (Apo-AI), apolipoprotein B

(Apo-B), lipoprotein(a) [Lp(a)], C-reactive protein (CRP), and PCSK9.

Secondary outcome

N/A

Study description

Background summary

The study drug ALN-PCSSC is a form of RNA (ribonucleic acid) that blocks the production of a protein called PCSK9. This protein is responsible for controlling the LDL-C levels in the blood. Lowering of the PCSK9 level in the blood has been shown in animals and people to result in lower LDL C in the blood.

LDL-C is also known as *bad cholesterol* as it is the type of cholesterol that causes a disease of blood vessels called atherosclerosis. Atherosclerosis is caused when too much cholesterol causes plaque to build up on the walls of the arteries (and veins) and the plaque can narrow or clog the arteries. Disease in blood vessels that supply the heart can cause heart attacks. In the brain it can cause strokes. In the legs it can cause pain and non-healing sores. Lowering cholesterol with lifestyle modifications (eg, quitting smoking and

improving diet) or with medications (eg, statins) has been shown to decrease the occurrence of strokes and heart attacks. However, as not all patients can be treated adequately, even with the currently available medications, there is a need for new drugs.

This medication is planned for use in patients with atherosclerotic heart disease, or people at risk for getting this disease because they have a family history of the disease or another disease such as diabetes.

Study objective

PRIMARY OBJECTIVE
The primary objective of this study is to evaluate the effect of ALN-PCSSC treatment on LDL-C levels at Day 180.

SECONDARY OBJECTIVES
The secondary objectives of this study are to evaluate the effect of ALN-PCSSC on the following:
* LDL-C levels at Day 90
* LDL-C levels at other time points
* PCSK9 levels over time
* other lipids, lipoproteins, apolipoproteins
* the proportion of subjects achieving different global lipid guidelines
* individual responsiveness to different doses
* duration of lipid-lowering effect of different doses
* the safety and tolerability profile of ALN-PCSSC

EXPLORATORY OBJECTIVES
To collect/evaluate the effect of ALN-PCSSC on the following:
* Cardiovascular (CV) events such as CV death, non-fatal myocardial infarction (MI), resuscitated cardiac arrest, and non-fatal stroke (ischemic and hemorrhagic)
* Evaluation of anti-drug antibodies (ADA) for the investigational product

Study design

This Phase II study is placebo-controlled, double-blind and randomized. This means that neither subjects or the study doctor will know if they receive study drug or placebo and in which dose. The study is performed in subjects who have been identified with atherosclerotic heart disease and subjects who are at risk for getting this disease or another disease such as diabetes.

All subjects who qualify for this study and agree to take part will be placed to receive either the investigational drug ALN-PCSSC or placebo (an injection that doesn*t contain any medication or active ingredient). Then subjects will be assigned to receive either a single does (one or two injections on day 1) or

two doses of treatment (one injection on day 1 and one on day 90).

Intervention

All subjects who qualify for this study and agree to take part will be placed to receive either ALN-PCSSC or placebo. Whether subjects receive one or two injections will depend on the group to which they are assigned as follows:

- Single dose (one or two injections on day 1)
- Two doses of treatment (one injection on day 1 and one on day 90).

Study burden and risks

As with any investigational treatment, side effects (unwanted experiences) cannot be totally predicted, and unexpected complications may occur.

However ALN-PCSSC has been previously tested in humans and was found to be generally safe and well-tolerated in subjects tested to date. Other drugs of the type used in this current study have also been found to be safe and well-tolerated in human subjects. In addition, ALN-PCSSC has also been previously tested in animals where there were no significant safety findings.

In the previous study in healthy volunteers, 51 subjects received single or multiple doses of ALN-PCSSC. In this study the drug was well tolerated with no serious side effects. The most common side effects in people who received one dose were cough, nasopharyngitis (cold-like symptoms), musculoskeletal (muscle and bone) pain, and rash. One mild local injection site reaction occurred at a dose of ALN-PCSSC that is higher than the doses planned for this study. The most common side effects in subjects who received more than one dose of ALN PCSSC were headache, back pain, diarrhea, and nausea. Three subjects had mild, local reactions at the site where they were injected. The total dose given in the previous study was more than patients will receive in this study.

Other side effects included indigestion, upper respiratory virus (common cold), and drowsiness. Due to limited data collected so far, these side effects may or may not be related to ALN-PCSSC. There were no significant abnormalities in blood pressure, pulse, ECGs, liver, or kidney laboratory tests. One subject had an abnormal liver test but other similar liver test results were all okay and the test result went back to normal after the subject stopped the study and other medications.

Injection reactions
ALN-PCSSC will be given under the skin (subcutaneous) in the abdomen and like with any injection given under the skin, patients could develop a reaction at the site of the injection. They could develop pain, tenderness, redness, swelling, itching, formation of sores, skin color changes, or other reactions

around an injection site. During the study, the study staff will check the site of injection for any reactions.

Allergic reactions
There is a remote chance that ALN-PCSSC (like any pharmaceutical product) may cause an allergic reaction, which in some cases can be severe - otherwise known as an anaphylactic reaction. This anaphylactic reaction may be characterized by sudden shortness of breath, decreased consciousness, and rash, and may require emergency treatment. Anaphylactic reactions have not been seen in animals who received ALN-PCSSC or in clinical trials where similar drugs to those used in this study were given to humans.

Risks associated with blood draws
There is a risk of minor discomfort, bruising, bleeding, swelling, or (rarely) infection at the site of needle insertion for blood drawing.

Risks associated with Placebo
Placebo will be injected subcutaneously in amounts similar to the amounts being injected for the active study drug (from 0.5 mL to 2.5 mL). No side effects are expected but like with any injection given under the skin, you could develop a reaction at the site of the injection.

Risks associated with ECG
Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.

Risks associated with Fasting
Fasting could cause dizziness, headache, stomach discomfort, or fainting

Reproductive Risks
The effects of ALN-PCSSC on the unborn child are unknown. It is not known if ALN-PCSSC could affect male sperm. There is no information on the long-term effects of ALN-PCSSC on fertility. In order to reduce the risk of pregnancy, female subjects of child-bearing potential must use two effective method of birth control while you are participating in this study. If you are already using a method of birth control, the study doctor or study staff will discuss with you whether your current method of birth control is acceptable for use during this study.

Acceptable birth control methods include, but are not limited to, oral contraceptives, barrier methods (diaphragm), approved contraceptive implant, long-term injectable contraception, intrauterine device (IUD) and tubal litigation (tubes tied).

Male subjects must agree to use an effective method of birth control during the entire study (i.e., condom with spermicide).

Contacts

Public
Medicines Company

Sylvan Way 8
Parsippany NJ 07054
US
Scientific
Medicines Company

Sylvan Way 8
Parsippany NJ 07054
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female subjects *18 years of age.
2. History of ASCVD or ASCVD-risk equivalents (symptomatic atherosclerosis, Type 2 diabetes, familial hypercholesterolemia, including subjects whose 10-year risk of a cardiovascular [CV] event assessed by Framingham Risk Score* or equivalent has a target LDL C of < 100mg/dL).
3. Serum LDL-C *1.8 mmol/L (*70 mg/dL) for ASCVD subjects or *2.6 mmol/L (*100 mg/dL) for ASCVD-risk equivalent subjects at screening.
4. Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening.
5. Calculated glomerular filtration rate >30 mL/min by estimated glomerular filtration rate (eGFR) using standardized local clinical methodology.
6. Subjects on statins should be receiving a maximally tolerated dose (investigator*s discretion).

7. Subjects on lipid-lower therapies (such as statin and/or ezetimibe) should be on a stable dose for *30 days before screening with no planned medication or dose change during study participation.
8. Willing and able to give written and informed consent before initiation of any study related procedures and willing to comply with all required study procedures.
*By Framingham Risk Score > 20%

Exclusion criteria

1. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk (according to investigator*s [or delegate] judgment) if he/she participates in the clinical study.
2. An underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate) might interfere with interpretation of the clinical study results.
3. New York Heart Association (NYHA) class II, III or IV heart failure or last known left ventricular ejection fraction <30%.
4. Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation.
5. Any history of hemorrhagic stroke.
6. Major adverse cardiac event within 6 months prior to randomization.
7. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite anti-hypertensive therapy.
8. Poorly controlled Type 2 diabetes, ie, glycated hemoglobin A1c (HbA1c) >10.0% prior to randomization.
9. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained alanine aminotransferase (ALT), aspartate aminotransferase (AST), elevation >2x the upper limit of normal (ULN), or total bilirubin elevation >1.5x ULN at screening confirmed by a repeat measurement at least 1 week apart.
10. Serious comorbid disease in which the life expectancy of the subject is shorter than the duration of the trial (eg, acute systemic infection, cancer, or other serious illnesses). This includes all cancers with the exception of treated basal-cell carcinoma occurring >5 years before screening.
11. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of contraception (oral contraceptives, barrier methods, approved contraceptive implant, long- term injectable contraception, intrauterine device or tubal litigation)**. Women who are >2 years postmenopausal defined as *1 year since last menstrual period AND if <55 years old with a negative pregnancy test within 24 hours of randomization or surgically sterile are exempt from this exclusion.
12. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
13. Known history of alcohol and/or drug abuse with the last 5 years.
14. Treatment with other investigational medicinal products or devices within 30 days or five half*lives, whichever is longer.

15. Use of other investigational medicinal products or devices during the course of the study.
16. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
a. Inappropriate for this study, including subjects who are unable to communicate or to cooperate with the investigator.
b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency).
c. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study).
d. Have any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the study.
e. Involved with, or a relative of, someone directly involved in the conduct of the study.
f. Any known cognitive impairment (eg, Alzheimer*s disease).
17. Previous or current treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.
**For the entire duration of the study

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:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-01-2016
Enrollment:	250
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ALN-PCSSC
Generic name:	ALN-PCSSC

Ethics review

Approved WMO Date:	17-11-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-12-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-06-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-08-2016
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	EUCTR2015-003772-74-NL
CCMO	NL55290.000.15