A randomized, double-blind, placebo controlled, first in human study to investigate the safety, tolerability, and pharmacokinetic and pharmacodynamic response of SLN360 in subjects with elevated lipoprotein (a)

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Ethical review	Approved WMO
Status	Completed
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON55119

Source
ToetsingOnline

Brief title
APOLLO

Condition

- Coronary artery disorders
- Congenital and hereditary disorders NEC
- Embolism and thrombosis

Synonym
atherosclerosis, elevated lipoprotein (a)

Research involving
Human

Sponsors and support

Primary sponsor: Silence Therapeutics plc
Source(s) of monetary or material Support: Industry - Silence Therapeutics plc

Intervention

Keyword: (atherothrombotic) cardiovascular diseases (CVD), lipoprotein(a) (Lp(a)), phase I, short interfering RNA (siRNA)

Outcome measures

Primary outcome

Safety and tolerability parameters of single or multiple doses SLN360 in

subjects with elevated Lp(a) levels.

Please see Appendices 2 and 3 of the protocol for detailed information on

safety and laboratory parameters.

Secondary outcome

PD and PK parameters of single and multiple doses of SLN360 on Lp(a).

Extent and duration of reduction in Lp(a) following single and multiple doses

of SLN360.

Impact of dose schedule of SLN360 on extent and duration of reduction in Lp(a).

Impact of single and multiple doses of SLN360 on lipid profile including apoB,

OxPLs, inflammatory markers, and plasminogen.

Please see Appendices 2 and 3 of the protocol for detailed information on

safety and laboratory parameters.

Study description

Background summary

The investigational medicinal product (IMP) SLN360 is a candidate siRNA medicine for the treatment of patients with conditions associated with raised Lp(a). SLN360 has the potential to address a major unmet medical need in this target subject population through targeted reduction of apo(a), a key component of the atherogenic Lp(a) particle. The preclinical pharmacology data support the use of SLN360 in subjects with raised Lp(a).

Study objective

The primary objective is:
i. To determine the safety and tolerability of single or multiple doses SLN360 in subjects with elevated Lp(a) levels.

The secondary objectives include assessment of the following:
i. PD effects of single and multiple doses of SLN360 on Lp(a).
ii. PK of SLN360 after a single and multiple dose administration.
iii. Extent and duration of reduction in Lp(a) following single and multiple doses of SLN360.
iv. Impact of dose schedule of SLN360 on extent and duration of reduction in Lp(a).

The exploratory objectives include assessment of the following:
i. Impact of single and multiple doses of SLN360 on lipid profile including apoB, OxPLs, inflammatory markers, and plasminogen.

Study design

Sentinel dosing will be employed for each cohort in the SAD: the first 2 subjects in each cohort will be randomised for 1 subject to receive active SLN360 and 1 subject to receive placebo. These two subjects will be dosed a minimum of 24 hours in advance of the rest of the subjects in the cohort.
For each cohort, safety and, where available, PK data will be reviewed and assessed by the SRC before recommending progression to the to the next dose escalation.

SAD:

Up to 5 cohorts, each consisting of of 8 subjects (6 active: 2 placebo) with elevated Lp(a) levels will be dosed at the appropriate dose level of SLN360 or placebo administered subcutaneously on Day 1. Subjects will be admitted as inpatients for dosing and for at least 24 hours of post-dose monitoring and assessment. The PD effects of SLN360 will be evaluated by measuring plasma Lp(a) levels as the most proximal measurable marker of target engagement. Effects on a broader lipid profile, including high density lipoprotein (HDL)-cholesterol, LDL-cholesterol and total cholesterol, triglyceride and apoB will also be measured. PK parameters will also be assessed at several timepoints for up to 36 hours after dosing. The SRC may recommend increasing the duration of follow-up beyond the currently planned 150 days, up to a maximum of 365 days.

MD:
Up to 3 cohorts, each consisting of 12 subjects (9 active: 3 placebo) with elevated Lp(a) levels will be treated with doses and at dose frequencies of SLN360 informed by data from the SAD part. Subjects will be admitted as inpatients for dosing and at least 24 hours of post-dose monitoring and assessment. Subjects will be followed for up to 201 days (duration informed by data from the SAD part) from the first dose to understand the magnitude and durability of the Lp(a) response to multiple dose administration of SLN360. As for the SAD cohorts, the PD effect of SLN360 will be evaluated by measuring plasma levels of Lp(a) and a range of other lipid fractions (LDL-cholesterol, HDLcholesterol, total cholesterol, triglyceride, and apoB). PK parameters will also be assessed at several timepoints after dosing. The final dose levels and dosing frequency of the MD cohorts will be dependent on safety, tolerability, PD and PK findings from the SAD part of the study

Please also refer to protocol section 3.

Intervention

SLN360 is a GalNAc conjugated 19-mer double stranded fully modified short interfering RNA (siRNA) targeting LPA messenger RNA (mRNA).
SLN360 will be provided as a solution for injection for s.c. use (200 mg/mL [as free acid form], presented as 0.5 mL extractable volume per vial).
Individual injection volume at each injection site will not exceed 1.5 mL, and up to 3 injection sites may be used to achieve the required dose.

Study burden and risks

physical examinations, hart monitoring, venapunctions, and subcutaneous injections are required for participants in this study. The venapunctions and injections have a risk of creating swelling or irritations. Unknown risks due to and allergic reactions to the study treatment are possible. Participants will have to spent additional time undergoing assessments and being monitored

in the hospital.

Opposed to these additional burdens are the potential benefit of the study treatment to participants and the gained scientific insights. Participants are drawn, and participate on an informed voluntary basis, from an applicable patient group with elevated Lp(a).

Contacts

Public
Silence Therapeutics plc

Hammersmith Road 72
London W14 8TH
GB
Scientific
Silence Therapeutics plc

Hammersmith Road 72
London W14 8TH
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

i. Male and female subjects aged 18 years to 70 years.
ii. Body mass index of >= 18 kg/m2 and <= 45 kg/m2.
iii. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and a negative pregnancy test (serum or urine) on

Day -1.
iv. All subjects must agree to adhere to appropriate contraception requirements (acceptable methods of contraception are summarized below and described in detail in the protocol), as follows:
a. WOCBP must agree to use 1 highly effective method of contraception, from the beginning of the screening period until 3 months after the last administration of study drug.
b. Male subjects must use a male condom (with or without spermicide) if sexually active with a female of child-bearing potential from the start of the screening period until 3 months after the last administration of study drug.
v. Male subjects are not allowed to donate sperm and female subjects are not allowed to donate eggs from the beginning of the screening period until 3 months following the last administration of SLN360.
vi. Subjects must provide written informed consent and be willing and able to comply with all study requirements.
vii. Elevated plasma Lp(a) = 150nmol/L
viii. For the MD part only: confirmed history of stable atherosclerortic cardiovascular disease (including, but not limited to, coronary artery disease with or without myocardial infarction, previous coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), ischaemic stroke, clinically important carotid artery stenosis, peripheral arterial disease). 'Stable' is defined as the absence of acute cardiovascular disease events within 6 months of screening (including, but not limited to, acute myocardial infarction, unstable angina, acute stroke, acute limb ischaemia).

Exclusion criteria

i. Comorbidity;
a. For the SAD part only: any history of clinically overt cardiovascular disease, defined as acute coronary syndromes, myocardial infarction, stable angina, coronary or other revascularization, ischemic stroke or transient ischemic attack and atherosclerotic peripheral arterial disease.
b. For the MD part only: recent history of acute cardiovascular disease events within 6 months of screening (including, but not limited to, acute myocardial infarction, unstable angina, acute stroke and acute limb ischemia).
c. Any uncontrolled or serious disease, or any medical or surgical condition including evidence of unstable cardiovascular disease, that may interfere with participation in the clinical study, significantly interfere with the interpretation of the results and/or put the subject at significant risk (according to Investigator*s judgement) if he/she participates in the clinical study.
d. Moderate or severe hepatic cirrhosis with Child-Pugh grade B or C, or other current or previous liver disease that may increase the risk of drug-induced liver injury or influence the pharmacology of SLN360.

e. Active serious mental illness or psychiatric disorder, including but not limited to schizophrenia, bipolar disorder, or severe depression requiring current pharmacological intervention.
f. Clinically significant illness within 7 days before the first dose of study drug.
g. Any conditions which, in the opinion of the Investigator, would make the subject unsuitable for enrolment in the study or could interfere with the subject*s participation in, or completion of the study.
h. Positive nucleic acid test for SARS-CoV-2 (the virus causing Covid-19) during screening.
i. Positive test for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti HBC), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV).

ii. Biochemical and hematological parameters:
a. Clinically significant abnormalities in screening blood tests (excluding lipid profile) that are judged to affect the suitability for inclusion, including:
i. ALT or AST >1.5 × ULN.
ii. Total bilirubin > ULN, except in previously confirmed cases of Gilbert*s syndrome.
iii. Platelet count < lower limit of the normal range.
iv. Significant renal impairment before randomization, defined as estimated glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration equation) <60 mL/min/1.73 m.
v. Haemoglobin A1c greater than 6.5% (47.5mmol/mol) in subjects without diabetes mellitus, or haemoglobin A1c greater than 8.5% (69.4mmol/mol) in subjects with diabetes mellitus and on appropriate diabetes treatment.

iii. Concomitant medication:
Subjects with previous or current use of the following therapies are not eligible for participation:
a. Medication or therapies significantly affecting Lp(a) level (including but not restricted to PCSK9 inhibitors, prescription dose niacin, fibrates or anti-estrogen therapy), unless on a stable dose or off treatment for >= 8 weeks prior to screening and no planned medication or dose adjustment during the study.
b. Statins and/or ezetimibe unless on a stable dose or off treatment for at least 8 weeks prior to screening and no planned medication or dose adjustment during the study.
c. Lipid or lipoprotein apheresis.
d. An investigational agent other than SLN360 within 90 days (or 10 half lives, whichever is longer) before the first dose of study drug.
e. Oligonucleotide therapy, including antisense oligonucleotides and siRNA, other than SLN360, within 12 months of screening.
f. Current use of hormone replacement therapy unless on a stable regimen or off treatment for at least 8 weeks prior to screening and no planned adjustment to

the regimen during the study.
g. Current use of anti-estrogen or estrogen receptor modulator (e.g. tamoxifen).

iv. Alcohol and illegal drugs:
a. History or clinical evidence of alcohol misuse within the 6 months before screening.
b. History or clinical evidence of illegal drug use within the 6 months before screening.

v. Drug intolerance:
a. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
b. History of intolerance to s.c. injections or scarring (e.g. from surgical procedures or burns) in skin areas where s.c. doses may need to be administered.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	22-02-2022
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO

Date:	29-07-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-12-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-11-2022
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	EUCTR2020-002471-35-NL
ClinicalTrials.gov	NCT04606602
CCMO	NL74573.000.20

Study results

Date completed: 24-01-2023

Results posted: 26-06-2024

First publication
03-04-2022