A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Phase 2 Study of ISIS 681257 Administered Subcutaneously to Patients with Hyperlipoproteinemia(a) and Established Cardiovascular Disease (CVD)

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To evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lp(a) levels in patients with hyperlipoproteinemia(a) and established CVD.To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON47033

Source
ToetsingOnline

Brief title
Phase 2 ISIS681257 in Patients With Hyperlipoproteinemia(a) and CVD

Condition

- Cardiac disorders, signs and symptoms NEC
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Disease of Heart and vessels. Elevated lipids

Research involving
Human

Sponsors and support

Primary sponsor: Akcea Therapeutics, Inc.
Source(s) of monetary or material Support: Ionis Pharmaceuticals;Inc.

Intervention

Keyword: Cholesterol, Heart, Lipoprotein

Outcome measures

Primary outcome

The primary efficacy endpoint is the percent change in Lp(a) from baseline at the primary analysis time point achieved by ISIS 681257 compared to pooled placebo.

Lp(a) levels will be analyzed from patient blood samples taken at specified time points throughout the study.

Secondary outcome

The secondary endpoints include the following parameters from baseline at the primary analysis

time point for ISIS 681257 compared to placebo:

* Percent change from baseline in LDL-C

* Proportion of patients who achieve plasma Lp(a) * 50 mg/dL (* 125 nmol/L)

* Proportion of patients who achieve plasma Lp(a) * 30 mg/dL (* 75 nmol/L)

* Percent change from baseline in apoB

* Percent change from baseline in OxPL-apo(a)

* Percent change from baseline in OxPL-apoB

Study description

Background summary

Fats like cholesterol are carried in the blood bound to special molecules called lipoproteins. Lipoproteins contain proteins and fats and contribute to fat transport, uptake and metabolism. One such lipoprotein is apolipoprotein(a) [apo(a)]. When apolipoprotein is bound to low density lipoprotein (LDL), the dominant carrier of cholesterol and also known as *bad cholesterol*, the molecule is referred to as lipoprotein(a), or Lp(a).
Elevation of Lp(a), called hyperliproteinemia(a), is genetically determined and may play a role in causing more aggressive forms of vascular disease which may therefore occur at an earlier age, with more frequency and progress more rapidly.
ISIS 681257 is a drug being developed to directly reduce the production of apo(a) by the liver and therefore the formation of Lp(a) with a view to potentially reduce the risk of recurrent or progressive disease in those patients with cardiovascular disease (CVD) associated with elevated Lp(a) levels in the blood. Such patients are at potential risk of early onset, progression and recurrence of arterial disease, such as hearts attacks, strokes, blockages of arteries in legs, associated with elevation of Lp(a).
This study is designed to test if ISIS 681257 can safely and effectively reduce Lp(a) and other lipoproteins in the blood, and to also determine the most effective dose and dosing frequency of ISIS 681257.

Study objective

To evaluate the safety, including tolerability, of ISIS 681257 and to assess the efficacy of different doses and dosing regimens of ISIS 681257 for reduction of plasma Lp(a) levels in patients with hyperlipoproteinemia(a) and established CVD.
To evaluate the efficacy of ISIS 681257 on plasma levels of low density lipoprotein cholesterol (LDL-C), apolipoprotein B100 (apoB), oxidized phospholipids (OxPL) on apo(a) [OXPL-apo(a)], and OxPL on apoB (OXPL-apoB).
To evaluate pharmacokinetics (PK) of ISIS 681257 across different doses and dose regimens in patients with hyperlipoproteinemia(a) and established CVD.

Study design

This is a Phase 2, randomized and double-blinded study that will be conducted at multiple study centers worldwide. This study will compare different dosing groups of ISIS 681257 and will also compare ISIS 681257 with a placebo, an inactive drug, to see if using ISIS 681257 is better than using a placebo.

If a patient is eligible to participate in this study he/she will be randomly

assigned to one of the dosing cohorts of the study which will include both ISIS 681257 and placebo, with different doses and different intervals of dosing. This assignment is done by chance, similar to drawing numbers out of a hat, such that some of the patients will receive ISIS 681257 and some will receive placebo in each of the dosing cohorts. Neither the patient, study doctor, nor study organizers will be able to choose or will know which form the patient is receiving or which dosing cohort they are assigned to. However, if necessary for a patient*s safety, the study doctor will have access to this information.

There will be five multiple-dose cohorts. The study drug will be administered by injection into the skin, also referred to as a subcutaneous injection, or SC. The usual site of injection is the abdomen or stomach region, but may also include the thigh or arm. The frequency of injections will depend on which dosing group the patient is randomly assigned to. In three of the cohorts study drug will be administered every four weeks (or once a month), in one cohort study drug will be administered every 2 weeks, and in one cohort study drug will be administered once per week. Each dose of study drug will be administered as one injection.

Below describes the frequency of dosing and total doses that may be administered in each cohort:

Cohort A to receive 0.2ml (20 mg ISIS 681257) or placebo Subcutaneous injection (SC) once every 4 weeks for up to 13 doses.

Cohort B to receive 0.4ml (40 mg ISIS 681257) or placebo SC once every 4 weeks for up to 13 doses.

Cohort C to receive 0.6ml (60 mg ISIS 681257) or placebo SC once every 4 weeks for up to 13 doses.

Cohort D to receive 0.2ml (20 mg ISIS 681257) or placebo SC every 2 week for up to 26 doses.

Cohort E to receive 0.2ml (20 mg ISIS 681257) or placebo SC every week for up to 52 doses

The study is divided into 3 periods, which are:
- A screening period of up to four (4) weeks,
- A dosing period of up to fifty-two (52) weeks, and
- A post-dosing follow-up period which will last sixteen (16) weeks.
During the treatment period, eligible patients will report to the study center for assessments at specified intervals throughout the treatment period, which is 6 months minimum duration and 52 weeks maximum in duration. Assessments and site visits are detailed in the Schedule of Procedures in Appendix A of the

protocol.
The treatment portion of the study will be complete when the last enrolled patient in the study reaches 6 months of exposure. All patients will then enter a 16-week post-treatment follow-up period, during which they will return to the Study Center for 3 follow-up visits 4, 10, and 16 weeks after their last injection of Study Drug as per Appendix A (Follow-up). There will be approximately 18 * 23 visits during the study depending on which dosing group a patient is to and depending on the length of the patient*s participation in the dosing period.
The final study visit for each patient will be 16 weeks after the last dose of Study Drug.
Research Biobank
During the study, blood samples will be frozen at several time points for analyses at a later time, but all related to the study objectives. Serum and plasma samples will be collected during the study and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of ISIS 681257. Blood samples will be kept for maximum of 15 years, and urine samples will be stored for up to a week after analyses are complete. Unused samples will be destroyed. No other tests will be performed without consent and approval from the Ethics Committee.

Intervention

N/A

Study burden and risks

Not all possible side effects of the study drug are known. The study treatment may prove to be less effective or to have more side effects than the other study treatment(s) or other available medication(s). The anticipated side effects listed below are based on animal studies, studies with patients with closely-related drugs, and studies with healthy volunteers with the ISIS 681257.
Reductions in platelets
In animal studies involving ISIS 681257 severe drops in platelet cell number were observed. Drops in platelet counts have also been seen with other closely-related drugs (a class of drugs called oligonucleotides) like ISIS 681257. Therefore, during this study, platelet count will be monitored every 2 weeks and the subject will not receive study drug unless a recent platelet count (within the prior 2 weeks) has been reviewed by the Study Doctor.
Flu-like Symptoms
Flu-like symptoms such as fever, chills, muscle aches, nausea, or vomiting have occurred in people taking drugs like ISIS 681257 and generally after the first or second dose. These events are typically reported as mild and resolved spontaneously either on the day of dosing or on the following day.

Inflammatory Reactions
Inflammation of the blood vessels (vasculitis) has been observed in animals administered oligonucleotide drugs like ISIS 681257 and risk of vasculitis cannot be excluded with ISIS 681257.
Kidney and Liver Function
Drugs like ISIS 681257 are known to reach their highest concentrations in the liver and kidney. In a clinical study of a closely related drug, there were two cases of the rare inflammatory kidney disease called crescentic glomerulonephritis, and one patient required long-term kidney dialysis. Therefore, during this study kidney function will be monitored every 2 weeks with blood and urine tests.
Animals and humans administered drugs like ISIS 681257 have experienced abnormalities in their liver function tests, indicating the possibility of liver damage. Therefore liver function will be monitored every 2 weeks for the first 3 months, and monthly thereafter in this clinical trial.
Injection Site Reactions
In other clinical trials with similar drugs that are also given by subcutaneous injections, local skin reactions can occur at the injection site. This reaction is typically a bruise or reddened area, but may include itching, swelling and/or a rash around the site of the injection. Typically, the reactions last less than a day or two. More severe reactions can last for up to a week.
Allergic Reaction Risks
As with taking any drug, there is a risk of allergic reaction.
Pregnancy and Reproductive Risks
The risks of ISIS 681257 to an embryo, fetus (unborn child), pregnancy, or to babies who are being breast-fed are unknown and therefore pregnancy should be actively avoided in study patients and their partners.
Clinical Study with ISIS 681257
ISIS 681257 has been evaluated in a Phase 1 study, ISIS 681257-CS1, in otherwise healthy volunteers with elevated Lp(a). The total exposures comprise 45 healthy subjects administered ISIS 681257 from 10 to 120 mg administered SC as a single-dose, or 10 to 40 mg as multiple doses (6 doses in 21 days). Subjects in this Phase 1 study received a total of 165 SC injections of ISIS 681257. The relatively small injection volumes and doses of ISIS 681257 were well-tolerated in the human volunteer study. There were no serious adverse events and the available safety data suggests that ISIS 681257 is not associated with any serious or severe safety findings. There were no clinically-relevant changes in laboratory assessments and all subjects completed the treatment and post-treatment evaluation periods.

Contacts

Public

Akcea Therapeutics, Inc.

Cambridge Parkway, Suite 100 Cambridge, 55
Cambridge MA 02142
US
Scientific
Akcea Therapeutics, Inc.

Cambridge Parkway, Suite 100 Cambridge, 55
Cambridge MA 02142
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Males or females aged * 18 and * 80 years old at the time of informed consent
3. Clinical diagnosis of CVD defined as documented coronary artery disease, stroke, or peripheral artery disease
4. Lp(a) plasma level * 60 mg/dL
5. Must be on standard-of-care preventative therapy for other than elevated Lp(a) CVD risk factors
6. Patients on the following medications must be on a stable regimen for at least 4 weeks prior to Screening and expected to remain on a stable regimen through the end of the post-treatment follow-up period:
a. Lipid lowering drugs (statins, ezetimibe, PCSK9 inhibitors, niacin, fibrates, fish oil or other products containing omega-3 fatty acids (including OTC preparations)
b. Antiplatelet drugs
c. Testosterone, estrogens, progesterone, growth hormone or progestins
7. Females: must be non-pregnant and non-lactating and either;

a. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy);
b. post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females * 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved);
c. Abstinent* or,
d. if engaged in sexual relations of child-bearing potential, agree to use 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 16 weeks after the last dose of Study Drug (ISIS 681257 or placebo)
* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception
8. Males must be surgically sterile or, if engaged in sexual relations with a female of child-bearing potential, the patient must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 16 weeks after the last dose of ISIS 681257

Exclusion criteria

1. Within 6 months of Screening: acute coronary syndrome, major cardiac surgery, or stroke/transient ischemic attack
2. Within 3 months of Screening: coronary, carotid, or peripheral arterial revascularization, major non-cardiac surgery, or lipoprotein apheresis
3. Heart failure NYHA class IV
4. Uncontrolled hypertension (systolic > 160 or diastolic > 100 mm Hg)
5. History of acute kidney injury within 12 months of Screening
6. Uncontrolled hyper or hypothyroidism
7. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
8. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
9. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
10. Patients with a history of major bleed or high-risk of bleeding diathesis
11. Recent history of, or current drug or alcohol abuse
12. Known history or presence of systemic allergic or pseudoallergic
(drug) reactions
13. Hypersensitivity to the active substance or to any of the excipients
14. Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following:
Clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following:
a. Urine protein/creatinine ratio (UPCR) * 0.25 mg/mg. In the event of a UPCR above this

threshold, eligibility may be confirmed by a quantitative total urine protein measurement of * 300 mg/24-hr
b. Urine albumin/creatinine ratio (UACR) * 100 mg/g. In the event of a UACR above this threshold, eligibility may be confirmed by a quantitative total urine albumin measurement of * 150 mg/24-hr
c. Estimated GFR * 60 mL/min as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) Equation for creatinine clearance
d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
> 2.0 x ULN
e. Bilirubin > ULN, unless prior diagnosis and documentation of Gilbert*s syndrome in which case total bilirubin must be * 3 mg/dL
f. Alkaline phosphatase (ALP) > ULN
g. Platelet count * LLN
15. Use of warfarin, direct thrombin inhibitors or factor Xa inhibitors
16. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
17. Treatment with any non-Ionis oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an Ionis oligonucleotide or siRNA within 9 months of screening. Patients that have previously received only 1-dose of an Ionis oligonucleotide as part of a clinical study may be included as long as * 4 months has elapsed since dosing
18. BMI > 40 kg/m2
19. Blood donation of 50-499 mL within 30 days of screening or of > 499 mL within 8 weeks of screening
20. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
21. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing 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):	13-07-2017
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Riboflavin (0.0015 mg), Sodium chloride (9.0 mg), Distilled Water for Injection (q.s. to 1.0 mL)
Generic name:	N/A
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-02-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-05-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-05-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-06-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-10-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-10-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-09-2018
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	EUCTR2016-003373-18-NL
CCMO	NL60047.000.17