A Randomized, Double Blind, Placebo-Controlled, Dose Titration, Phase 2 Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ISIS 494372 Administered Subcutaneously to Patients with High Lipoprotein(a)

Published: 07-07-2014
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Primary Objectives:-To characterize the safety and tolerability of ISIS 494372 in individual patients at escalating doses of 100, 200, and 300 mg/week-To characterize the efficacy of ISIS 494372 in lowering Lp(a) using a dose titration study design....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON42290

Source
ToetsingOnline

Brief title
ISIS 494372-CS3

Condition

- Lipid metabolism disorders

Synonym
High lipoprotein(a)

Research involving
Human

Sponsors and support

Primary sponsor: ISIS Pharmaceuticals
Source(s) of monetary or material Support: Isis Pharmaceuticals

Intervention

Keyword: High Lipoprotein(a), ISIS 494372, LDL

Outcome measures

Primary outcome

Serum Lp(a) levels will be assessed following SC administration of Study

Drug (ISIS 494372 or placebo).

Secondary outcome

Levels of oxidized phospholipids associated with apoB, Lp-PLA2, lipid panel,

systemic markers of inflammation and plasminogen/coagulation markers as

well as any changes in isoform size will be assessed following SC

administration of Study Drug (ISIS 494372 or placebo).

Study description

Background summary

ISIS 494372 is a second-generation antisense oligonucleotide (ASO) drug targeted to apo(a). It binds to mRNA which results in the Ribonuclease H (RNase H)-mediated degradation of the apo(a) mRNA, thus preventing production of the apo(a) protein. This will result in a reduction of the lipoprotein(a) level. It has been hypothesized that a pharmacologic reduction in Lp(a) could slow down or reverse cardiovascular disease by reducing thrombotic, atherogenic or inflammatory events in patients with elevated Lp(a) levels.

Study objective

Primary Objectives:
-To characterize the safety and tolerability of ISIS 494372 in individual patients at escalating doses of 100, 200, and 300 mg/week
-To characterize the efficacy of ISIS 494372 in lowering Lp(a) using a dose titration study design.

Exploratory Objectives:
-To determine the pharmacodynamic effects of ISIS 494372 vs. placebo on oxidized phospholipids associated with apoB-100, Lp-PLA2, lipoprotein(a) isoform size, lipid panel, systemic markers of inflammation, and plasminogen/coagulation markers.

Study design

Randomized, double-blind, placebo-controlled,phase 2, dose-titration multi-center
study

Intervention

Cohort A (n = 50): Patients will be randomized 1:1 to receive ISIS 494372 or placebo.
Cohort B (n = 10): Patients will be randomized 4:1 to receive ISIS 494372 or placebo.

In both cohorts, patients will receive a SC dose of either 100 mg ISIS 494372 or placebo on Days 1, 8, 15 and 22, a SC dose of either 200 mg ISIS 494372 or placebo on Days 29, 36, 43, and 50, and a SC dose of either 300 mg ISIS 494372 or placebo on Days 57, 64, 71 and 78.

Patients may be down titrated from 200mg or 300mg to a lower dose if they fail to tolerate the higher dose.

Study burden and risks

Risks: possible side effects of the study drug.

Burden: 19 visits at the Study doctor, blood and urine samples are taken during each visit and also vital signs will be checked . Study drug or placebo will be administered during 12 visits.

Contacts

Public

ISIS Pharmaceuticals

Gazelle Ct. 2855
Carlsbad 92010
US
Scientific
ISIS Pharmaceuticals

Gazelle Ct. 2855
Carlsbad 92010
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 18-75 inclusive
3. Satisfy the following:
a. Females: non-pregnant and non-lactating, surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy),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), abstinent or if engaged in sexual relations of child-bearing potential, subject is using an acceptable contraceptive method (see 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
b. Males must be surgically sterile, abstinent 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 Study Drug

4. BMI *40 kg/m2
5. Lipoprotein(a) *125 and <438 nmol/L (*50 and >175 mg/dL) at time of screening (Cohort A) Lipoprotein(a) * 438 nmol/L (* 175 mg/dL) at time of screening (Cohort B)

Exclusion criteria

1. Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of screening, major surgery within 3 months of screening) or physical examination
2. Clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion, including the following:
a. Urine protein/creatinine (P/C) ratio *0.2 mg/mg. In the event of a P/C ratio above this threshold, eligibility may be confirmed by a quantitative total urine protein measurement of <150 mg/24 hr
b. Positive test (including trace) for blood upon urinalysis. In the event of a positive test, eligibility may be confirmed with a urine microscopy showing *5 red blood cells (RBCs) per high power field
c. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 x ULN
d. Bilirubin > ULN. Patients with Gilbert*s syndrome (elevated indirect bilirubin with normal direct bilirubin and normal ALT and AST) may be eligible after discussion with Medical Monitor
e. Alkaline phosphatase, serum creatinine or BUN > ULN
f. Platelet count 3.Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
4.Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
5.Known history or positive test for human immunodeficiency virus (HIV), hepatitis C, or chronic hepatitis B
6.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
7.Treatment with another Study Drug, biological agent, or device within one month of screening, or 5 half-lives of study agent, whichever is longer
8.Treatment with any non-ISIS oligonucleotide (including siRNA) at any time or prior treatment with an ISIS oligonucleotide or siRNA within 9 months of screening. Patients that have previously received only one dose of an ISIS oligonucleotide as part of a clinical study may be included as long as *4 months has elapsed since dosing.
9.History of bleeding diathesis or coagulopathy
10.Recent history of, or current drug or alcohol abuse
11. Use of statins, ezetimibe, niacin, fish oil or other products containing omega-3 fatty acids (including OTC preparations)or fibrates unless on a stable regimen for at least 8 weeks prior to screening and will remain on a stable regimen through the end of the Post-Treatment Evaluation Period
12. Use of testosterone, estrogens, progesterone or progestins unless on a stable regimen for at least 8 weeks prior to screening and will remain on a stable regimen through the end of the Post-Treatment Evaluation Period
13. Patients who are currently receiving apheresis to reduce elevated levels of lipids

14. Use of concomitant drugs (including herbal or OTC medications other than ibuprofen, paracetamol, topical aspirin based analgesics, antihistamine, or topical steroids * 1% hydrocortisone) unless authorized by the Sponsor Medical Monitor
15. Blood donation of 50-499 mL within 30 days of screening or of > 499 mL within 8 weeks of screening
16. Have any other conditions, which, in the opinion of the Investigator 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):	29-01-2015
Enrollment:	34
Type:	Actual

Ethics review

Approved WMO

Date:	07-07-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	04-12-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-02-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-02-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-05-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-07-2015
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	EUCTR2014-000701-13-NL
ClinicalTrials.gov	NCT02160899
CCMO	NL49457.000.14