A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ISIS 416858 (IONIS-FXIRX an Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis

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Primary objectives: To evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ISIS 416858 (200, 250, and 300 mg once weekly) as compared to placebo.Exploratory Objectives: Incidence of myocardial infarction (MI), stroke, systemic...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46462

Source
ToetsingOnline

Brief title
ISIS 416858-CS5

Condition

- Other condition
- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
Blood Clotting during blood dialysis, Coagulopathy during hemodialysis

Health condition

End-Stage Renal Disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: End-Stage Renal Disease, Hemodialyse, ISIS 416858, Thrombosis

Outcome measures

Primary outcome

Safety and Tolerability Evaluations

The safety and tolerability of ISIS 416858 will be assessed by determining the incidence and severity of adverse events (including bleeding events) and changes in laboratory evaluations.

The primary safety outcome is the combination of major bleeding (MB) and clinically-relevant non-major bleeding (CRNMB) during the treatment period (or early study termination).

Secondary outcome

Other safety parameters including (S)AEs, deaths, vital signs, ECG and laboratory parameters will also be recorded. This may include additional information regarding events of interest (i.e. bleeding events, thrombotic events).

Pharmacokinetic Evaluations

Plasma pharmacokinetics will be assessed following the first and last dose in the PK subgroup, whenever possible. Additionally, plasma trough and post-treatment samples will be collected during treatment and post-treatment evaluation period, respectively, for the measurement of ISIS 416858 concentrations.

Pharmacodynamic Evaluations

Coagulation parameters such as FXI activity and antigen, aPTT, PT and INR will be monitored throughout the treatment and post-treatment evaluation period visits.

The rate/frequency of clotting on the dialysis filters and circuit will be measured as an exploratory analysis.

Study description

Background summary

ISIS 416858 is a 2*-methoxyethyl chimeric antisense inhibitor of the molecular target Factor XI (FXI). FXI is a plasma glycoprotein that is synthesized primarily in the liver. Preclinical studies suggest that FXI inhibitors can prevent venous and arterial thrombosis without affecting hemostasis, and congenital FXI-deficient patients have a low incidence of ischemic stroke and venous thromboembolism (VTE) (Schumacher et al. 2010). Thus, selective inhibition of FXI may represent a novel approach for the prevention of undesired thrombotic events such as VTE and ischemic stroke as well as clotting of hemodialysis circuits which limits the effectiveness of hemodialysis.

Study objective

Primary objectives: To evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ISIS 416858 (200, 250, and 300 mg once weekly) as

compared to placebo.

Exploratory Objectives: Incidence of myocardial infarction (MI), stroke, systemic embolism, and cardiovascular (CV) mortality.

Study design

This is a Phase 2, multi-center, stratified, randomized, double-blind, placebo-controlled study of ISIS 416858 (IONIS-FXIRX an Antisense Inhibitor of Factor XI) treatment for up to 26 weeks in ESRD patients receiving hemodialysis at least 3 times a week.

Subjects included in this study will maintain all of their standard of care dialysis treatments (including heparins) as determined by their treating practitioners.

Subjects will be stratified based on the diagnosis of documented atrial fibrillation at Screening, and then subjects will be randomized to 1 of 3 dose cohorts in a 1:1:1 ratio (Cohort A, Cohort B, and Cohort C). Within each dose cohort, subjects will be randomized in a 3:1 ratio to receive subcutaneous treatment with either ISIS 416858 or placebo.

Cohorts A, B, and C
Patients in Cohort A will be randomized to receive once weekly either 200 mg ISIS 416858 or placebo, subjects in Cohort B will be randomized to receive either 250 mg ISIS 416858 or placebo, and Cohort C will be randomized to receive either 300 mg ISIS 416858 or placebo.

The study will include a 4-week screening period and a 26-week treatment period followed by a 12-week post-treatment evaluation period.

Upon completion of screening evaluations, including SC tolerability assessments with 0.9% sterile saline injections, eligible subjects will receive Study Drug (ISIS 416858 or placebo) once weekly for the 26-week treatment period. All doses of Study Drug will be administered subcutaneously (SC) after completion of the hemodialysis treatment and within 2 hours (preferably within 15 minutes).

Intervention

on the diagnosis of documented atrial fibrillation and then randomized to 1 of 3 dose cohorts in a 1:1:1 ratio (Cohort A, Cohort B, and Cohort C). Within each dose cohort, subjects will be randomized in a 3:1 ratio to receive subcutaneous treatment with either ISIS 416858 or placebo that is added to standard of care hemodialysis therapies as prescribed by their providers, including heparin.

Cohort A: Approximately 68 dialysis subjects will be randomized 3:1 to either 200 mg ISIS 416858 or placebo
Cohort B: Approximately 68 dialysis subjects will be randomized 3:1 to either 250 mg ISIS 416858 or placebo
Cohort C: Approximately 68 dialysis subjects will be randomized 3:1 to either 300 mg ISIS 416858 or placebo

The SC Tolerability assessments using 0.9% sterile saline will be administered as two 0.75 mL noncontiguous injections on Study Days S-14 (± 3) and S-7 (± 3).

For Cohort A, B and C, the Sponsor will provide ISIS 416858 (200 mg/mL, 1.0 mL) and Placebo (1.0 mL). All doses are given by SC injection.

ISIS 416858 or placebo will be administered SC post-dialysis session within 2 hours (preferably within 15 minutes) once each week for a total of 26 consecutive weeks of treatment in all cohorts.

The injection volume will be 1.0 mL for Cohort A (200 mg), 1.25 mL for Cohort B (250 mg) and 1.5 mL for Cohort C (300 mg). Cohorts B and C will be administered Study Drug (ISIS 416858 or placebo) as two noncontiguous SC injections.

Study burden and risks

ISIS 416858 has been evaluated in 4 clinical studies: (1) A study in 66 healthy volunteers in which treatment was given up to 6 weeks (ISIS 416858-CS1 study); (2) A combination study in healthy volunteers with another blood thinner drug that is made from heparin called enoxaparin (a blood thinner also known as Lovenox) in 14 healthy volunteers for up to 5 weeks (ISIS 416858-CS2 study); (3) A study in which treatment was administered for up to 6 weeks in 232 subjects that had total knee replacement surgery (ISIS 416858-CS3 study); (4) a study in which 36 subjects with end-stage renal disease on hemodialysis were administered treatment for up to 12 weeks (ISIS 416858-CS4 study).

ISIS 416858 at doses from 50 mg to 300 mg was well tolerated in the healthy volunteers and did not cause any bleeding events. For subjects in the ISIS 416858-CS3 study, treatment with the 300 mg dose of the study drug significantly reduced blood clotting without any increase in bleeding events after the major surgery on the knee as compared to standard treatment with enoxaparin. In subjects with end-stage renal disease on hemodialysis in the ISIS 416858-CS4 study, treatment with 200 and 300 mg doses of the study drug was generally safe and well-tolerated and the results suggested a reduction in severe dialysis circuit clotting. To date, only one serious side effect (allergic reaction) has been reported as related to ISIS 416858, and the person quickly and completely recovered within 2 days and required no further treatment.

Oligonucleotide compounds, the same type of compounds as ISIS 416858 are known

to reach their highest concentrations in the liver and kidney. Therefore, your liver function will be monitored thoroughly throughout the study. Based on the results of the previous clinical trials in over 336 subjects, ISIS 416858 at the multiple dose range of 50-300 mg did not affect liver and kidney function. Thus, it is expected that ISIS 416858 at dose levels used in this study will not affect your liver and kidney function.

The most common side effects in the previous studies were mild adverse events at the subcutaneous injection site. Typically, this includes mild redness that may be accompanied by pain, bruising, discoloration, itching, and/or swelling at the injection site. These events at the injection site are typically mild and normally disappear spontaneously within a week on their own. In general, the reactions do not appear to worsen with repeated dosing or result in any generalized effects in the body.

The potential for bleeding to happen due to this blood thinner that decreases factor XI levels is a risk. However, in subjects with congenital (existing at or before birth) factor XI deficiency, no spontaneous bleeding has been reported. Bleeding symptoms in surgical settings have been investigated in subjects with congenital factor XI deficiency. Mild bleeding typically can occur after surgery or injuries to areas such as the mouth, nose and genitourinary (genital and urinary) system. Additionally, there is a risk that ISIS 416858 treatment may not prevent the formation of blood clots in the dialysis circuit that may occur during hemodialysis. However, in this study, you will be checked for potential clots by the study staff so that if needed, you can be treated immediately. You will also be continued on your regular medications that are prescribed by your dialysis providers, such as heparin during hemodialysis so that blood clots do not occur.

Decreasing factor XI levels with ISIS 416858 has not been associated with increased bleeding risk in any of the studies completed to date. For example, no bleeding without a known cause (spontaneous) has been observed in the previous clinical studies even in subjects in whom factor XI levels were reduced by more than 80% to almost undetectable levels for several weeks. Subjects receiving hemodialysis can be at a high risk of blood clotting as well as bleeding events. You will be observed carefully for all possible side effects.

In previously conducted animal studies, ISIS 416858 was given at similar or higher doses to what you will receive. The only serious side effect observed in these animal studies was a low occurrence of severe platelet decrease (reduced amount of blood cells that help blood clot) for which ISIS 416858 treatment had to be stopped or treatment with corticosteroids (a treatment that increases platelet levels) had to be initiated. Due to low platelet counts 2 out of the 16 animals in the highest dose group did not continue the study and were put to sleep. These platelet reductions were not associated with any major bleeding.

Minor bleeding events have reported in subjects treated with ISIS 416858 and with placebo. Most of the minor bleeding events involved bleeding at the indwelling catheter site, the administration and blood sampling site or on the skin, and most subjects did not have symptoms and did not require treatment. The minor bleeding events were not associated with a reduction in FXI levels.

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

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 to 85 years old at the time of informed consent.
a. Females: must be non-pregnant and non-lactating and either:
i. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral

oophorectomy);
ii. 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); or,
iii. if engaged in sexual relations and of child-bearing potential, agree to use 2 highly effective contraceptive methods from the time of signing the informed consent form until at least 84 days (approximately 5 half-lives of ISIS 416858) after the last dose of Study Drug (ISIS 416858 or placebo).
b Males: Surgically sterile or if engaged in sexual relations with a female of child-bearing potential, subject is utilizing an acceptable contraceptive method from the time of signing the informed consent form until at least 84 days (approximately 5 half-lives of ISIS 416858) after the last dose of Study Drug (ISIS 416858 or placebo).
3. End stage renal disease maintained on outpatient hemodialysis at a healthcare center for > 3 months from screening with hemodialysis at least 3-times per week for a minimum of 9 hours per week of prescribed treatment time and plan to continue this throughout the study.

Exclusion criteria

1. Subjects with a history of a major medical event (e.g., previous acute coronary syndrome, stroke or transient ischemic attack, or systemic thromboembolic event) within 3 months of screening, major surgery within 3 months of screening, or new major physical examination finding (not accounted for by past medical history), except for documented atrial fibrillation.
2. Active bleeding (as judged clinically significant by the Investigator) within the past 3 months from screening or documented bleeding diathesis (excluding uremia), coagulopathy, or recent history of prolonged compression time at arteriovenous fistula.
3. Screening laboratory results as follows:
* Platelet count < 150,000 cells/mm3
* < 180,000 cells/mm3 for platelet function/activation subgroup
* INR > 1.4
* aPTT > upper limit of normal (ULN)
* FXI activity < 0,3 U/ml
* ALT or AST > 2 x ULN
* Total bilirubin > ULN
4. Subject is not willing to have weekly subcutaneous injections over the study period as assessed during screening.
5. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 (first dose) or IV antibiotic use at the time of Screening.
6. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.
7. Known history of or positive test at Screening for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B.
8. 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. Subjects with a history of other malignancies that have been treated with curative intent and which have no recurrence

within 5 years may also be eligible if approved by the Sponsor Medical Monitor (or designee).
9. Treatment with another investigational drug, biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent, whichever is longer.
10. Any history of previous treatment with an oligonucleotide (including siRNA). Subjects that have previously received only a single-dose of an ISIS-oligonucleotide as part of a clinical study may be included as long as a duration * 4 months has elapsed since dosing.
11. Attending nephrologist answers "no" to the question, "Would you be surprised if this patient died in the next year?"
12. Within 6 months prior to screening, have any of the following:
* More than 3 episodes of severe hypoglycemia requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions
* One (1) event of hypoglycemia in which the patient required hospitalization
* Recurrent syncope and recurrent hypotension in the inter-dialytic period requiring intervention
13. Planned major surgery in the next 6 months, including subjects receiving a kidney transplant or subjects that anticipate changing dialysis modality (i.e. hemodialysis to peritoneal dialysis).
14. Recent history of, or current drug or alcohol abuse as determined by the Investigator.
15. Concomitant use of anticoagulant/antiplatelet agents (e.g., warfarin, dabigatran, rivaroxaban, clopidogrel) that may affect coagulation (except low dose aspirin (* 100 mg/day)) during Treatment and Post-treatment Evaluation Periods is not allowed. Stable doses of heparins during dialysis are permitted.
16. Uncontrolled hypertension as judged by the Investigator. For example, subjects with a pre- or post-dialysis blood pressure (BP) that is > 180 mmHg on at least 3 of the last 5 dialysis treatments.
17. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject 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:	Completed
Start date (anticipated):	27-07-2018
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	12-09-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-01-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-05-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-08-2018
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)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-03-2019
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	EUCTR2017-002165-21-NL
CCMO	NL62709.000.17

Study results

Date completed:	12-06-2019
Results posted:	14-07-2020

First publication

10-07-2020