A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of ISIS 304801 Administered Subcutaneously to Patients with Hypertriglyceridemia

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Primary Objective(s):To evaluate the efficacy of ISIS 304801 as compared to placebo on the percent change in fasting triglycerides (TG) from baseline.Secondary Objectives:To evaluate the efficacy of ISIS 304801 as compared to placebo on the...

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

Summary

ID

NL-OMON43654

Source
ToetsingOnline

Brief title
ISIS CS-16 / Compass

Condition

- Lipid metabolism disorders

Synonym
hypertriglyceridemia

Research involving
Human

Sponsors and support

Primary sponsor: IONIS Pharmaceuticals, Inc

Source(s) of monetary or material Support: ISIS Pharmaceuticals;Inc.

Intervention

Keyword: apoC-III, Hypertriglyceridemia, ISIS 304801

Outcome measures

Primary outcome

Efficacy evaluations include percent change from baseline and absolute change from baseline as compared with placebo in fasting TG as well as other lipid parameters, and measures of insulin sensitivity for ISIS 304801 as compared to placebo. Analysis of response will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

The primary endpoint is the % change in fasting TG from baseline as measured at the primary analysis time point.

Secondary outcome

_Absolute change from baseline in fasting TG

_Proportion of patients who achieve * 40% reduction from baseline in fasting TG

_Percent change from baseline in HDL-C

_Proportion of patuents who achieve fasting TG < 150mg/dL

_Change from baseline in HOMA-IR

_Change from baseline in HbA1c in T2DM patients

Study description

Background summary

Severe Hypertriglyceridemia is a serious disease and is the result of both primary (genetic) as well as secondary factors including obesity, inadequately treated diabetes, insulin resistance, alcohol and some drugs. One of the major clinical risks of markedly elevated triglycerides (TG) levels is acute pancreatitis. According to the NCEP ATPIII Guidelines (2002) severe hypertriglyceridemia (fasting TG levels * 500 mg/dL) is accompanied by an increasing risk for acute pancreatitis, a risk that increases with increasing TG levels. While the development of pancreatitis may occur at TG levels > 500 mg/dL, the risk of pancreatitis is considered clinically significant if TG levels exceed 880 mg/dL (10 mmol/L), levels at which chylomicrons are considered to predominate.

Prospective case studies have provided evidence that interventions that lower fasting TG (drug treatment or plasmapheresis) can reduce or eliminate pancreatitis relapse in patients with severe Hypertriglyceridemia and a significant history of recurrent pancreatitis. Although not the primary goal of treatment of patients with severe Hypertriglyceridemia, lowering of TG in these patients may have additional benefits on the risk of cardiovascular events.

Other studies reported that lowering TG in a patient population with initial TG > 500 mg/dL was associated with a dose-dependent reduction in new cardiovascular events. In addition, hypertriglyceridemia is widely believed to impair insulin sensitivity and lowering of elevated TG is an essential component of therapy of diabetic patients. Results from a Phase 2 study of ISIS 304801 in T2DM patients (Study ISIS 304801-CS4) indicated that, in addition to profound TG lowering effects, ISIS 304801 could have a positive impact on multiple measures of glycemic control (fructosamine, glycated albumin and HbA1c) and peripheral insulin sensitivity (multiple measures assessed during a hyperinsulinemic-euglycemic clamp study).

Study objective

Primary Objective(s):

To evaluate the efficacy of ISIS 304801 as compared to placebo on the percent change in fasting triglycerides (TG) from baseline.

Secondary Objectives:

To evaluate the efficacy of ISIS 304801 as compared to placebo on the following:
_Absolute change from baseline in fasting TG
_Proportion of patients who achieve * 40% reduction from baseline in fasting TG
_Percent change from baseline in HDL-C
_Proportion of patients who achieve fasting TG < 150mg/dL
_Change from baseline in HOMA-HR
_Change from baseline in HbA1c in T2DM patients

Tertiary/Exploratory Objectives:

To evaluate the effect of ISIS 304801 as compared to placebo on:
_Percent change from baseline in fasting apolipoprotein C-III (total apoC-III, HDL-apoC-III, LSL-apoC-III and very low density lipoprotein-apoC-III [VLDL-apoC-III])
_Other fasting lipid measurements, including: non-HDL-C, apoB, apoA-1, VLDL-C, and LDL-C
_Lipoprotein particle size/number
_Change from baseline in fasting plasma glucose, fructosamine and glycated albumin in T2DM patients
_Percent change from baseline in fasting apoB-48 and chylomicron-TG

Safety Objectives:

_To evaluate the safety and tolerability of ISIS 304801
_To evaluate the effects of ISIS 304801 as compared to placebo on prospectively adjudicated actue pancreatitis events (Atlanta classification) and Major Adverse Cardiovascular Events (MACE)

Study design

This is a multi-center, double-blind, placebo-controlled study.

After an up to 8-week screening period, including at least a 6-week diet stabilization period, eligible patients will be randomized in 2:1 to receive 300mg ISIS 304801 or placebo, respectively.
All patients will receive 26 doses of Study Drug by SC injection once a week for 26 weeks.
Following the Week 26 visit, patients will enter the 13 week post-treatment evaluation period.

The primary end point for the study will be evaluated after the last patient has completed the Week 26/ET visit and will be assessed based on the percent change from baseline in fasting TG at the primary analysis time point (Month 3).

Intervention

Cohort A (n=70) ISIS 304801
Cohort B (n=35) Placebo

Patients will be randomized in 2:1 to receive 300mg ISIS 304801 or placebo, respectively.

Study burden and risks

Risks: possible side effects of the study drug

Burden:
*14 visits at the studycenter, during each visit the patient needs to come fasted (not allowed to eat or drink, except water, anything for at least 10 hours in advance of the visit)
*During each visit bloodsamples will be taken
*During 6 visits urine samples will be collected
*During 9 visits vital signs will be measured
*During the entire study, the patient needs to follow a strict low fat diet and can't drink any alcohol or use drugs

Contacts

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations by law
2. Age * 18 years at time of informed consent
3. BMI * 45kg/m²
4. Stable weight (+/- 4kg) for >6 weeks prior to screening
5. Fasting TG * 500mg/dL (* 5.7mmol/L)at Screening. If the fasting TG value at Screening is < 500mg/dL (< 5.7mmol/L) but *350mg/dL (* 4.0mmol/L) up to two additional tests may be performed in order to qualify
6. If on statin or fibrate, patients must be on stable, labeled dose for at least 3 months prior to screening that is not anticipated to change during the study treatment period. Patients not receiving these drugs within 4 weeks prior to screening are also eligible.
7. Fasting TG * 500mg/dL at Qualification Visit. IF fasting TG is < 500mg/dL but * 350mg/dL (* 4.0mmol/L) up to two additional tests may be performed in order to qualify.
8. Willing to maintain their customary activity level and to follow the NCEP ATP III TLC diet or similar with weight maintenance during the study.
9. Satisfy one of 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 ameorrhea in females > 55 years of age or, in females * 55 years, 12 months of spontaneous ameorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations and of child-bearing potential, patient is using an acceptable contraceptive method from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration
b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method from the time of signing the informed consent form until 13 weeks after the last dose fo Study Drug administration.
* 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

Exclusion criteria

1. Type 1 diabetes mellitus
2. Type 2 Diabetes mellitus with any of the following:
a. Newly diagnosed within 12 weeks of screening
b. HbA1c * 9.0% at Screening
c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of +/- 10 units of insulin])
d. Anticipated need to change dose or type of medication during the treatment period of the

Study (with the exception of +/- 10 units of insulin)
e. Current use of GLP-1 agonists, if patient has history of pancreatitis
3. Acute pancreatitis within 3 months of screening
4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening
5. Any of the following laboratory values at Screening:
a. Hepatic: Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be * 3mg/dL; ALT > 2.0x ULN; AST > 2.0 x ULN
b. Renal: Persistently positive (2 out of 3 tests * 1+) for protein on urine dipstick. In the event of positive test eligibility may be confirmed by a quantative total urine protein measurement of < 500mg/24hrs; Persistently positive (2 out of 3 tests * trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing * 5 red blood cells per high power field; Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50mL/min
c. Cardiac troponin I > ULN at Screening
d. LDL-C > 130mg/dL (> 3.4 mmol/L) at Screening for all patients and LDL-C > 100mg/dL (> 2.6 mmol/L) for patients with T2DM or history of MACE
e. any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion
6. Uncontrolled hypothyroidism (abnormal thyroid function tests should be approved by Study medical monitor)
7. Uncontrolled hypertension (BP > 160/100 mm Hg)
8. History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at Screening
9. History of heart failure with NYHA greater than Class II
10. History of gastrointestinal malabsorption (e.g., uncontrolled Crohn's disease, etc.) or history of a gastric bypass or other diversional bariatric surgery
11. Gastric banding procedure within 1 year of screening
12. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
13. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
14. 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
15. Treatment with another investigational drug, biological agent, or device within one month of screening, or 5 half-lives of investigational agent, whichever is longer
16. History within 6 months of screening of drug or alcohol abuse
17. Unwilling to comply with lifestyle requirements
18. Use of any of the following medications:
a. Omega-3 fatty acids (prescription or OTC preparations) within 4 weeks of screening unless on a stable dose for at least 4 weeks prior to screening and dose, brand and regimen expected to remain constant throughout the study
b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening
c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless

approved by Sponsor medical monitor
d. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant throughout the study
e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant throughout the study
f. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed
g. Anti-obesity drugs (e.g., orlistat, lorcaserin, phentermine/topiramate combination, herbal preparations, phentermine, amphetamines) within 12 weeks prior to screening
h. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study
i. Prior exposure to ISIS 304801
j. Any other medications unless stable at least 4 weeks prior to screening (occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)
19. Blood donation of 50 to 499mL within 30 days of screening or of > 499mL within 60 days of screening
20. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)
21. Have any other conditions, which, in the opinion of the Investigator or the 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:	3
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):	29-06-2015

Enrollment:	12
Type:	Actual

Ethics review

Approved WMO Date:	09-12-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-03-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-09-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-09-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-03-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-05-2016

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2016
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:	06-07-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-09-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-09-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-10-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-10-2016
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	EUCTR2014-003434-93-NL
ClinicalTrials.gov	NCT02300233
CCMO	NL51524.000.14

Study results

Date completed: 29-12-2016

Actual enrolment: 6

Summary results
Trial is onging in other countries