A Randomized, Double-Blind, Placebo-Controlled, with an Open Label Extension, Phase 2/3 Study of volanesorsen Administered Subcutaneously to Patients with Familial Partial Lipodystrophy

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Primary Objective:To evaluate the efficacy of volanesorsen for reduction in severity of metabolic derangement in patients with FPL with hypertriglyceridemia and uncontrolled diabetes.Secondary Objectives:To evaluate the safety and tolerability of...

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

Summary

ID

NL-OMON44784

Source
ToetsingOnline

Brief title
ISIS CS 17 / BROADEN

Condition

- Lipid metabolism disorders

Synonym
Familial Partial Lipodystrophy

Research involving

Human

Sponsors and support

Primary sponsor: IONIS Pharmaceuticals Inc.
Source(s) of monetary or material Support: IONIS Pharmaceuticals Inc.

Intervention

Keyword: apoC-III, Familial Partial Lipodystrophy, volanesorsen

Outcome measures

Primary outcome

The effect of volanesorsen as compared to placebo on the percent change from

Baseline in fasting triglycerides (TG) at Month 3

Secondary outcome

_Change from Baseline in hepatic steatosis (as assessed by hepatic fat fraction

using magnetic resonance imaging [MRI])

_Change from Baseline in hemoglobin A1c (HbA1c)

_Change from Baseline in liver volume and hepatic steatosis (as assessed by

magnetic resonance imaging [MRI])

_ A composite endpoint at Month 6 for percent of patients who achieve

a. * 40% reduction in fasting TG, and

b. * 30% reduction of hepatic fat fraction percent

_ Change in patient-reported outcomes (PRO):

o Disease burden score

o Patient-reported pain

o Patient-reported hunger

o Quality of life

Study description

Background summary

Familial Partial Lipodystrophy (FPL) is a rare genetic condition characterized by selective loss of adipose tissue that leads to fat deposition in the liver and muscle and the development of insulin resistance, diabetes and fatty liver disease. People with FPL have high amounts of fats called triglycerides in their blood which may result in multiple medical conditions including pancreatitis.
Current treatments includes lifestyle modification such as reducing caloric intake and increasing energy expenditure via exercise. Conventional therapies used to treat sever insulin resistance and/or high TGs are not very efficacious in these patients. Furthermore, patients with FPL have a higher chance to receive a diagnosis for diabetes.

Volanesorsen is designed to reduce the amount of apolipoprotein C-III (apoC-III, a protein found in blood). Reducing the amount of apoC-II in blood may help people lower the amount of triglycerides (TG) too. By reducing apoC-III and TG levels, volanesorsen may improve the metabolic profile of patients with FPL and reduce their risk of acute pancreatitis. In addition, apoC-II inhibition may also improve insulin sensitivity in these patients and potentially lead to a reduction in the complications associated with diabetes.

Study objective

Primary Objective:
To evaluate the efficacy of volanesorsen for reduction in severity of metabolic derangement in patients with FPL with hypertriglyceridemia and uncontrolled diabetes.

Secondary Objectives:
To evaluate the safety and tolerability of volanesorsen in patients with FPL.
To further evaluate the role of serum TGs in modulating insulin resistance in FPL patients and the impact of TGs reduction on adipose tissue distribution in FPL patients.

Study design

This is a multi-center, randomized, double-blind, placebo-controlled study with an Open Label Extension
The study will comprise the following periods:
1.Screening: An up to 6-week Screening period, including diet stabilization phase.
2.Randomization treatment period: Following stabilization, up to 60 eligible

patients will be randomized 1:1 to receive volanesorsen 300mg or placebo once weekly for 52 weeks. Patients will be educated on drug administration.
3. Open-Label Extension period: all patients will receive volanesorsen for up to 104 weeks
4. Follow up period of 13 weeks

Intervention

Cohort A (n=30): volanesorsen
Cohort B (n=30): Placebo

Patients will be randomized in 1:1 to receive 300mg volanesorsen or placebo respectively.

In the Open-label extension period all patients will receive volanesorsen

Study burden and risks

Risks: possible side effects of the study drug and study procedures

Burden: multiple visits to the study center

*Patients are required to fast from all food and drink (except water) for at least 10 hours (max 12 hours) before each visit
*During the whole study, alcohol intake must be limited and patients will need to refrain from drinking any alcohol for at least 48 hours prior to each study visit
*Patients need to follow a stable diet moderate in carbohydrates and fats and maintain their customary physical activity level
*Patients will be asked to complete the 'hunger and Widespread Pain' Questionnaire weekly
*Patients who suffer from diabetes are required to daily monitor their blood glucose via the SMBG (Self-Monitoring Blood Glucose)

*During max 14 visits, an ECG will be done
*During max 7 visits an echocardiogram and an MRI will be done
*During max 4 visits a DEXA scan will be performed
*Blood will be drawn, the platelet counts will be checked weekly
*Urine samples will be collected
*Skinfold measurements will be conducted

Contacts

Public

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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 give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age * 18years at the time of informed consent
3. Clinical diagnosis of familial partial lipodystrophy plus diagnosis of type 2 diabetes mellitus and hypertriglyceridemia.
4. A diagnosis of type 2 diabetes mellitus as defined by the International Diabetes Federation guidelines of 2012, made at least 6 months prior to the Screening, and
* A HbA1c * 7% to * 12% at Screening,
* On anti-diabetic therapy consisting of:
a. Metformin * 1500 mg/day, or
b. If the dose of metformin is < 1500 mg/day, or metformin is not tolerated, then the patient should be on other oral anti-diabetic drugs (OAD) or an injectable glucagon-like peptide-1 (GLP-1) receptor agonist, or
c. Insulin therapy alone or in combination with other anti-diabetic drugs;5.Hypertriglyceridemia is defined as Fasting TG levels * 500mg/dL (*5.7mmol/L) at Screening and Qualification Visit.

Patients with the clinical diagnosis of FPL and with Fasting TG levels * 200 (* 2.26 mmol/L) to < 500 mg/dL (* 5.7 mmol/L) at both Screening and Qualification Visits who meet the genetic or family history criteria for study inclusion may be further screened and enrolled in the study.
6. Presence of hepatosteatosis (fatty liver), as evidenced by a Screening MRI indicating a hepatic fat fraction (HFF) * 6.4%
7. Willing to maintain their customary physical activity level and to follow a diet moderate in carbohydrates and fats with a focus on complex carbohydrates and replacing saturated for unsaturated fats.
8. Satisfy one (1) of the following:
a. Females: Non-pregnant and non-lactating; surgically sterile (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopaudal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females * 55years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone (FSH) levels in the postmenopausal range for the laboratory involved), abstinent, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method from time of signing the informed consent form until at least 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 at least 13 weeks after the last dose of Study Drug administration

Exclusion criteria

1. A diagnosis of generalized lipodystrophy
2. A diagnosis of acquired partial lipodystrophy (APL)
3. Acute pancreatitis within 4 weeks 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 heart failure requiring a change in medication
5. Major surgery within 3 months of Screening
6. history of heart failure with New York Heart Association functional classification (NYHA) greater than Class II or unstable congestive cardiac failure requiring a change in medication
7. Uncontrolled hypertension (blood pressure [BP] >160 mm Hg systolic and/or 100 mm Hg diastolic)
8. Any of the following laboratory values at Screening:
a. Cardiac troponin I > upper limit of normal (ULN)
b. LDL-C > 130mg/dL on maximal tolerated statin therapy
c. Hepatic: Total bilirubin >ULN; Alanine aminotransferase (ALT) > 3.0xULN; Aspartate aminotransferase (AST) > 3.0xULN
d. Renal: 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; Two (2) out of three (3) consecutive tests * 1+ for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a

quantitative total urine protein measurement of < 1.0g/24hrs; Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 60mL/min
e.Platelet count < lower limit of normal (LLN)
f. Clinically significant (as determined by the Investigator or Sponsor) abnormalities on laboratory examination that will increase risk to the patient or interfere with data integrity
9. Uncontrolled hypothyroidism (abnormal thyroid function tests should be approved by Study Medical Monitor)
10. History within 6 months of Screening of drug or alcohol abuse
11. History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at 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 durg, biological agent, or device within one (1) month of Screening, or 5 half-lives of investigational agent, whichever is longer
16. Unwilling to comply with lifestyle requirements
17. Use of any of the following:
a. Metreleptin within the last 3 months prior to Screening
b. Antidiabetic, lipid lowering, or atypical antipsychotic medication, unless on a stable dose for at least 3 months prior to Screening
c. insulin unless on a stable daily insuling dose regime (±20%) for at least 4 weeks prior to dosing
d. GLP-1 agonists within 4 weeks prior to dosing, if patient has a history of pancreatitis
e. Nicotinic acid or derivates of nicotinic acid within 4 weeks prior to screening
f. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Screening unless approved by the Sponsor Medical Monitor
g. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to dosing
h. 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
i. oral anticoagulants unless on a stable dose for at least 4 weeks prior to dosing and regular clinical monitoring is performed
j. Anti-obesity drugs within 12 weeks prior to screening
k. Prior exposure to volanesorsen
l. Any other medication unless stable at least 4 weeks prior to dosing (occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)
18. Blood donation of 50 to 499mL within 30 days of Screening or of >499mL within 60 days of Screening
19. 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:	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):	06-06-2016
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	15-09-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-12-2015
Application type:	First submission
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:	21-07-2016
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:	24-01-2017
Application type:	Amendment
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:	06-07-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-01-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-01-2018
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-02-2018
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	EUCTR2015-000493-35-NL
CCMO	NL54058.000.15