AAV8-mediated Low Density Lipoprotein Receptor (LDLR) Gene Replacement in Subjects with Homozygous Familial Hypercholesterolemia (HoFH)

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The primary objective will be to determine the safety of AAV8.TBG.hLDLR administration in this patient population. The secondary objective is to assess the efficacy of LDL-C reduction achieved with AAV8.TBG.hLDLR administration.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Inborn errors of metabolism
Study type	Interventional

Summary

ID

NL-OMON47467

Source
ToetsingOnline

Brief title
AAV8.TBG.hLDLR for FH

Condition

- Inborn errors of metabolism

Synonym
familial hypercholesterolaemia

Research involving
Human

Sponsors and support

Primary sponsor: REGENXBIO Inc

Source(s) of monetary or material Support: National Heart;Lung;and Blood Institute (NHLBI)

Intervention

Keyword: AAV8, Gene Replacement, HoFH, LDLR

Outcome measures

Primary outcome

Primary Objectives

To determine the safety of AAV8.TBG.hLDLR administration in patients with homozygous familial hypercholesterolemia (HoFH) as assessed by the number of reported adverse events, changes noted on physical examinations, and clinical laboratory parameters assessed up to 24 weeks post vector administration.

Secondary outcome

2.2. Secondary Objectives

-* To assess the LDL-C reduction achieved with AAV8.TBG.hLDLR administration as defined by percent change in LDL-C at 12 weeks (Cohort 1 only) or 18 weeks after vector administration (or 4 weeks after steroid termination or prior to changing lipid lowering therapies) compared to baseline.

-* To assess changes in other lipid parameters at 12 weeks (Cohort 1 only) or 18 weeks after vector administration (or 4 weeks after steroid termination or prior to changing lipid lowering therapies) compared to baseline values, specifically percent change in total cholesterol (TC), non-high density lipoprotein cholesterol (non-HDL-C), HDL-C, fasting triglycerides (TG), very low density lipoprotein cholesterol (VLDL-C), lipoprotein(a) (Lp(a)), apolipoprotein B (apoB), and apolipoprotein A-I (apoA-I).

-* To determine the safety of AAV8.TBG.hLDLR administration as assessed by the number of reported adverse events, changes noted on physical examinations and clinical laboratory parameters assessed at multiple time points up to 104 weeks post vector administration.

-* To assess vector shedding in plasma and urine.

2.3. Exploratory Objectives

-* To assess the immune response to the vector administration.

-* To assess the metabolic mechanism by which LDL-C is reduced by performing LDL kinetic studies prior to vector administration and again 12 weeks (Cohort 1 only) or 18 weeks after vector administration (or 4 weeks after steroid termination or prior to changing lipid lowering therapies). The primary parameter to be evaluated is the fractional catabolic rate (FCR) of LDL apoB.

-* To assess the percentage of subjects achieving various LDL-C thresholds (e.g., LDL-C <200, <130, or <100, mg/dl) after treatment with AV8.TBG.hLDLR, combined with the use of adjunctive treatments over the duration of the study.

-* To assess the need for reintroduction or initiation of lipid lowering therapy after treatment with AAV8.TBG.hLDLR, including frequency of LDL apheresis.

-* Assess treatment interaction between PCSK9 inhibitors and AAV8.TBG.hLDLR (e.g., synergistic LDL-C reduction)

-* Reduction in number, size, or extent of assessable xanthomas compared to baseline.

Study description

Background summary

The correction of the hypercholesterolemia observed in patients with HoFH that underwent liver transplant (Ibrahim et al. 2012, Kucukkartallar et al. 2011) underscores the importance of the liver in regulating the levels of circulating lipid and lipoproteins. Thus a gene therapy approach that focuses on delivering the correct transgene to the liver may represent a viable approach. The investigational agent is an AAV8 vector expressing the transgene human low density lipoprotein receptor, (hLDLR) under control of a liver-specific promoter (thyroxine-binding globulin, TBG).

Study objective

The primary objective will be to determine the safety of AAV8.TBG.hLDLR administration in this patient population. The secondary objective is to assess the efficacy of LDL-C reduction achieved with AAV8.TBG.hLDLR administration.

Study design

This is a sequential, open-label, single, ascending dose study of AAV8.TBG.hLDLR for the treatment of adults with homozygous familial hypercholesterolemia (HoFH) carrying two mutations in the LDLR gene. The design utilizes a half-log increase in AAV dose and a formal safety assessment of the lower dose group prior to dose escalation. The trial will involve three cohorts. A standard *3+3* Phase 1 dose-escalation is used with 3 subjects per dose level, potentially expanding to 6 subjects per level in the event of dose-limiting toxicity (DLT) at any level, and with provision to expand up to an additional 3 subjects at the recommended dose to better characterize the optimal dose and rate of toxicity at that level. Dosing between consecutive subjects within a dose cohort will be allowed only after the appropriate safety assessment at the 4 weeks post-dosing visit is completed. Dosing will be separated by a minimum of 6 weeks between cohorts to ensure adequate assessment of potential short-term toxicity and appropriate review by the data safety monitoring board (DSMB).

Intervention

AAV8.TBG.hLDLR will be administered via a peripheral vein by infusion.

Study burden and risks

Potential risks associated with the administration of AAV8.TBG.hLDLR; Vector-induced hepatitis and hepatotoxicity; Other risks; Risks Associated with

Withdrawal of Lipid-lowering Treatment or steroid treatment.
Risk/benefit assessment based on all available information appear to be acceptable with the potential for a clinically significant LDL lowering accompanied by relatively low probability of serious toxicity.

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. Male or female * 18 years of age.
2. Untreated and/or treated LDL-C levels and clinical presentation consistent with the diagnosis of homozygous FH
3. Molecularly defined LDLR mutations at both LDLR alleles.
4. Concurrent allowed lipid lowering medication must be stable for * 4 weeks before the baseline visit and must remain stable until 18 weeks after vector administration (or 4 weeks

post steroid termination). These include but are not limited to: statins, ezetimibe, bile acid sequestrants, PCSK9 inhibitors, and LDL and/or plasma apheresis. Subjects on other lipid-lowering medications are eligible for the study but must wash out of these medications for the pre-specified time period.
5. Females of childbearing potential must have a negative pregnancy test at screening and baseline visits and be willing to have additional pregnancy tests during the study.
6. Sexually active subjects (both female and male) must be willing to use a medically accepted
method of contraception from screening visit until 6 months after vector administration
7. A baseline serum AAV8 NAb titer * 1:10.

Exclusion criteria

1. Unwilling to wash out of the following lipid lowering therapies for the pre-specified time period:
a. niacin > 250 mg/day: within 6 weeks of baseline
b. fibrates: within 4 weeks of baseline
c. lomitapide: within 8 weeks of baseline
d. mipomersen: within 24 weeks of baseline
2. Heart failure defined by the NYHA classification as functional Class III with history of hospitalization(s) within 12 weeks of the baseline visit or functional Class IV.
3. History within 12 weeks of the baseline visit of a myocardial infarction (MI), unstable angina leading to hospitalization, coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), uncontrolled cardiac arrhythmia, carotid surgeryor stenting, stroke, transient ischemic attack, carotid revascularization, endovascular procedure or surgical intervention.
4. Uncontrolled hypertension defined as: systolic blood pressure > 180 mmHg, diastolic blood pressure > 95 mmHg.
5. Uncontrolled diabetes defined as HbA1c > 8.5% or an average fasting glucose * 160 mg/dl.
6. Known hypersensitivity to prednisone
7. History of cirrhosis or chronic liver disease based on documented histological evaluation or non-invasive imaging or testing.
8. Documented diagnosis of any of the following liver diseases:
a. Nonalcoholic steatohepatitis (biopsy-proven)
b. Alcoholic liver disease
c. Autoimmune hepatitis
d. Liver cancer
e. Primary biliary cirrhosis
f. Primary sclerosing cholangitis
g. Wilson*s disease
h. Hemochromatosis
i. *1 anti-trypsin deficiency
9. Abnormal liver function tests (LFTs) at screening (AST or ALT > 2 × upper limit of normal (ULN) and/or Total Bilirubin of * 1.5 × ULN unless patient has unconjugated hyperbilirubinemia due to Gilbert*s syndrome).

10. Hepatitis B as defined by positive for HepB SAg, or Hep B Core Ab, and/or viral DNA
11. Chronic active Hepatitis C as defined by positive for HCV Ab and viral RNA.
12. History of chronic alcohol abuse within 52 weeks of the screening visit.
13. Certain prohibited medications known to be potentially hepatotoxic, especially those that can induce microvesicular or macrovesicular steatosis. These include but are not limited to: Accutane (isotretinoin), amiodarone, HAART medications, heavy acetaminophen use (2 g/day more than 3 times a week), isoniazid, methotrexate, tetracyclines, tamoxifen, or valproate.
14. Active tuberculosis, systemic fungal disease, or other chronic infection.
15. History of immunodeficiency diseases, including a positive HIV test result.
16. Chronic renal insufficiency defined as estimated GFR < 30 mL/min/1.73m2.
17. History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer.
18. Previous organ transplantation.
19. Administration of an investigational drug within 12 weeks or 5 half-lives of the drug (whichever is longer) prior to the screening visit and until 52 weeks after receivingAAV8.TBG.hLDLR. Subjects are not prohibited from receiving investigational drugs after
52 weeks.
20. Any major surgical procedure occurring less than 3 months prior to the screening visit, or any planned future surgical procedure within 3 months of baseline.
21. Serious or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise the subject*s safety or successful participation in the study.
22. Any other medical condition or finding that would make it not in the subject*s best interest
to participate in the study
23. Study staff member or any direct family member.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-12-2017

Enrollment:	2
Type:	Actual

Ethics review

Approved WMO Date:	23-08-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-09-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-12-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-11-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-05-2019

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-05-2020
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	EUCTR2016-001446-25-NL
CCMO	NL57533.000.16