An Open-Label, Single-Arm, Multicenter Pilot Study to Evaluate Safety, Tolerability, and Efficacy of ALN-PCSSC in Subjects with Homozygous Familial Hypercholesterolemia

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PrimaryTo characterize the effect of 90 and 180 days of subcutaneous ALN-PCSSC on the percentage change from Day 1 inlow-density lipoprotein cholesterol (LDL-C) in subjects with homozygous familial hypercholesterolemiaSecondary* To assess the effect...

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

Summary

ID

NL-OMON45636

Source
ToetsingOnline

Brief title
ORION-2

Condition

- Inborn errors of metabolism

Synonym
Homozygous Familial Hypercholesterolemia, hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: The Medicines Company
Source(s) of monetary or material Support: The Medicines Company

Intervention

Keyword: ALN-PCSSC, Familial Hypercholesterolemia, Homozygous, Open-Label

Outcome measures

Primary outcome

To characterize the effect of 90 and 180 days of subcutaneous ALN-PCSSC on the

percentage change from Day 1 in

low-density lipoprotein cholesterol (LDL-C) in subjects with homozygous

familial hypercholesterolemia

Secondary outcome

* To assess the effect of ALN-PCSSC on:

* Absolute change and percentage change in LDL-C from Day 1 to each subsequent

visit until Day 180 or

final visit

* Absolute change and percentage change in PCSK9

* Absolute change and percentage change in total cholesterol, triglycerides,

HDL-C, non-HDL-C, VLDL-C,

Apo-A1, Apo-B and Lp(a) from Day 1 to each subsequent visit until Day 180 or

final visit

* To evaluate the safety and tolerability of ALN-PCSSC in subjects with

homozygous familial

hypercholesterolemia

Study description

Background summary

Elevated LDL-C has been shown in multiple studies to be one of the major risk factors for coronary heart disease (CHD) with a continuous and graded relationship between plasma LDL-C concentration and CHD risk. In addition, a large meta-analysis of 21 statin studies concluded that for every 1 mmol/L (39 mg/dL) reduction in LDL-C (with statin therapy) there is an approximate 22% reduction in cardiovascular events. While statins are the treatment of choice for hyperlipidemia and the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) there is still a need for additional lipid-lowering therapies for patients who do not reach target LDL-C levels. Furthermore, in many patients, statin therapy cannot be optimized as patients are either intolerant of statins due to side effects or because of other adverse effects such as elevations in liver enzymes. Thus, there remains a clear unmet medical need for lowering LDL-C, especially in certain patient populations.

Study objective

Primary
To characterize the effect of 90 and 180 days of subcutaneous ALN-PCSSC on the percentage change from Day 1 in low-density lipoprotein cholesterol (LDL-C) in subjects with homozygous familial hypercholesterolemia
Secondary
* To assess the effect of ALN-PCSSC on:
* Absolute change and percentage change in LDL-C from Day 1 to each subsequent visit until Day 180 or final visit
* Absolute change and percentage change in PCSK9
* Absolute change and percentage change in total cholesterol, triglycerides, HDL-C, non-HDL-C, VLDL-C, Apo-A1, Apo-B and Lp(a) from Day 1 to each subsequent visit until Day 180 or final visit
* To evaluate the safety and tolerability of ALN-PCSSC in subjects with homozygous familial hypercholesterolemia
Exploratory:
* To evaluate the formation of Anti-drug antibodies (ADA) to ALN- PCSSC
* To assess response of LDL-C by underlying causal mutations of homozygous familial hypercholesterolemia (HoFH)

Study design

This study will be a Phase II, open label, single arm, multicenter pilot study in subjects with homozygous familial hypercholesterolemia.

Intervention

The study drug (ALN-PCSSC) will be administered by subcutaneous (SC) injection

Study burden and risks

Diet, fasting before the blood draws

Contacts

Public
The Medicines Company

8 Sylvan Way
Parsippany NJ 07054
US
Scientific
The Medicines Company

8 Sylvan Way
Parsippany NJ 07054
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adolescents (12-15 years)
Adolescents (16-17 years)

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

Inclusion criteria

1. Males and females, * 12 years of age with a diagnosis of homozygous familial hypercholesterolemia by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration >500 mg/dl (13 mmol/L) together with either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents. ;2. Stable on a low-fat diet ;3. Stable on their pre-existing, lipid-lowering therapies (such as statins, cholesterol-absorption inhibitors, bile-acid sequestrants, or combinations thereof) for at least 4 weeks with no planned medication or dose change for the duration of study participation ;4. Fasting central lab LDL-C concentration >130 mg/dl (3.4 mmol/L) and triglyceride concentration < 400 mg/dL (4.5 mmol/L), ;5. Bodyweight of 40 kg or greater at screening. ;6. Subjects should be willing and able to give written informed consent before initiation of any study-related procedures (if the subject is less than 18 years of age, written consent will be obtained from their guardian or legally authorized representative, with verbal assent from the child).

Exclusion criteria

1. LDL or plasma apheresis within 8 weeks prior to the screening visit, and no plan to receive it during the study because of the attendant difficulty in maintaining stable concentrations of LDL-C while receiving apheresis.;2. Use of Mipomersen or Lomitapide therapy within 5 months of screening.;3. Previous treatment with monoclonal antibodies directed towards PCSK9 within 8 weeks of screening.;4. New York Heart Association (NYHA) class III or IV heart failure or last known left ventricular ejection fraction < 30% or any cardiac arrhythmia within past 3 months that is not controlled by medication.;5. Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 3 months of enrollment;6. Planned cardiac surgery or revascularization;7. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg despite anti-hypertensive therapy.;8. Poorly controlled diabetes mellitus, i.e., glycated hemoglobin A1c (HbA1c) >10.0%.;9. Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m2;10. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained alanine aminotransferase (ALT), aspartate aminotransferase (AST), elevation > 3x the upper limit of normal (ULN), at screening confirmed by a repeat measurement at least 1 week apart.;11. Creatine kinase (CK) > 5x ULN without a known cause;12. Other serious comorbid disease in which the life expectancy of the subject is shorter than the duration of the trial (e.g., acute systemic infection or other serious illnesses).;13. Any history of malignant disease, with the exception of treated basal-cell carcinoma occurring >5 years before screening.;14. Females who are pregnant or nursing, or who are of childbearing potential (includes adolescent females who have reached menarche and are sexually active) and unwilling to use at least two methods of contraception (e.g., oral contraceptives, barrier methods, approved contraceptive implant, long- term injectable contraception, intrauterine device) for the entire duration of the study. Exemptions

from this criterion:;a. Women >2 years postmenopausal (defined as 1 year or longer since their last menstrual period) AND more than 55 years of age ;b. Postmenopausal women (as defined above) and less than 55 years of age with a negative pregnancy test within 24 hours of enrollment ;c. Women who are surgically sterilized at least 3 months prior to enrollment;d. Adolescent females who have not reached menarche;15. Males who are unwilling to use an acceptable method of birth control during the entire study period (e.g., condom with spermicide).;16. Known history of alcohol and/or drug abuse within 5 years.;17. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:;a. Inappropriate for this study, including subjects who are unable to communicate or to cooperate with the investigator.;b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency).;c. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study).;d. Have any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the study.;e. Involved with, or a relative of, someone directly involved in the conduct of the study.;18. Any clinically significant disease or condition affecting a major organ system, including but not limited to gastrointestinal, renal, hepatic, endocrinologic, pulmonary, neurological, metabolic or cardiovascular disease.;19. Any surgical or medical condition which, in the judgment of the Investigator, might interfere with the pharmacokinetics, distribution, metabolism, or excretion of the study drug (if applicable).;20. Treatment with other investigational medicinal products or devices within 30 days or 5 half-lives, whichever is longer, prior to the administration of the study drug, planned use of investigational medicinal products or devices.;21. Previous participation in this study or any preceding study with ALN-PCSSC.;22. Hypersensitivity to any of the ingredients of the study drug being used.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	09-02-2018
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO Date:	09-01-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-06-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-02-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-03-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-04-2018
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	EUCTR2016-003376-49-NL
CCMO	NL59772.000.16