Open-Label Extension Study of EFC12492, R727-CL-1112, EFC12732 and LTS11717 Studies to Assess the Long-Term Safety and Efficacy of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia

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Primary objective* To assess the long-term safety of alirocumab when added to currently available lipid-modifying drug therapy in patients with heterozygous familial hypercholesterolemia (heFH) who have completed one of the following studies:...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON45050

Source
ToetsingOnline

Brief title
ODYSSEY OLE

Condition

- Metabolic and nutritional disorders congenital
- Lipid metabolism disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Familial hypercholesterolemia, inherited disorder of lipid metabolism

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Sanofi-Aventis

Intervention

Keyword: Alirocumab, Familial, Heterozygous, Hypercholesterolemia

Outcome measures

Primary outcome

The primary endpoint of this study is safety.

Safety Endpoints:

* Safety parameters (adverse events, laboratory data, vital signs) assessed

throughout the OLE study.

Primary objective

* To assess the long-term safety of alirocumab when added to currently

available lipid-modifying drug therapy in patients with heterozygous familial

hypercholesterolemia (heFH) who have completed one of the following studies:

EFC12492, R727-CL-1112, EFC12732 & LTS11717.

Secondary outcome

Efficacy Endpoints of interest include:

* Calculated serum LDL-C values and percent changes from baseline of the parent

study (EFC 12492, R727-CL-1112, EFC 12732 or LTS11717) over time in this study.

* Proportion of patients achieving an LDL-C < 100 mg/dL (2.59 mmol/l) over time

in this study.

* Proportion of patients achieving an LDL-C < 70 mg/dL (1.81 mmol/L) over time in this study.

* Proportion of patients with LDL-C <70 mg/dL (1.81 mmol/L) and/or *50% reduction from baseline of the parent study in LDL-C (if LDL-C *70 mg/dL [1.81 mmol/L]) over time in this study.

* Values and percent changes from baseline of the parent study in other lipids and other lipoproteins, including total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), HDL-C, triglycerides (TGs), apolipoprotein (Apo) B, ApoA-1, ApoB/ApoA-1 ratio and Lp(a) over time in this study.

Other Endpoints:

* Anti-alirocumab antibodies assessed throughout the study.

* Proportion of patients who were up-titrated to 150 mg of alirocumab based on Investigator*s judgment.

* Proportion of patients who were down-titrated to 75 mg of alirocumab based on Investigator*s judgment.

* Reasons (ie, LDL-C threshold, AE) that trigger a down-titration or an up-titration of alirocumab.

* EQ-5D summary scores.

Secondary objectives

* To evaluate the long-term efficacy of alirocumab on lipid parameters.

* To evaluate the long term immunogenicity of alirocumab.

Study description

Background summary

This open-label extension study will include patients diagnosed with heterozygous familial hypercholesterolemia (heFH) who have completed EFC12492, R727-CL-1112, EFC12732 or LTS11717.

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism that predisposes a person to premature severe cardiovascular disease (CVD). Familial hypercholesterolemia has a high prevalence in Caucasian populations, where an estimated 1 in 500 individuals are affected. Defects in at least 3 different genes that code for proteins involved in hepatic clearance of low density lipoprotein-cholesterol (LDL-C) can cause FH. These include mutations in the gene coding for the LDL receptor (LDL-R) that removes LDL-C from the circulation, and less commonly, in the gene for Apo B, which is the major protein of the LDL particle. In rare cases, the gene coding for proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme involved in degrading the LDL-R (gain of function mutation), is mutated. In all cases, this results in an accumulation of LDL-C in the plasma from birth, and subsequent development of tendon xanthomas, xanthelasmas, atheromata, and premature CVD.

In the heterozygous form of FH (heFH), the cumulative risk of experiencing a coronary event by the age of 60 years without effective treatment is at least 50% in men and approximately 30% in women (coronary disease occurs approximately 10 years later in women than in men, with a marked increase in post-menopausal women). Before effective treatment with 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (commonly referred to as statins) became available, mortality from coronary disease was increased by nearly 100 fold in young FH adults aged 20 to 39 years, and approximately 4 fold for FH patients aged 40 to 59 years.

In the real world, a large proportion of patients with FH do not reach treatment goals and, by consequence, remain at increased risk of CVD. In a recent large cross-sectional study conducted in the Netherlands, nearly all heterozygous FH patients (96%) were on statin treatment. Only 21% of patients achieved the LDL-C goal of less than 100 mg/dL (less than 2.59 mmol/L) and about 5% of patients still had an LDL-C concentration greater than 200 mg/dL. Among those not at goal, 27% were on combination therapy of maximum statin dose and ezetimibe. These data emphasize the need for new LDL-lowering therapies.

Study objective

Primary objective
* To assess the long-term safety of alirocumab when added to currently available lipid-modifying drug therapy in patients with heterozygous familial hypercholesterolemia (heFH) who have completed one of the following studies: EFC12492, R727-CL-1112, EFC12732 & LTS11717.

Secondary objectives
* To evaluate the long-term efficacy of alirocumab on lipid parameters.
* To evaluate the long term immunogenicity of alirocumab.

Study design

This is a Phase 3, open-label extension (OLE), uncontrolled study.

Patients must have been diagnosed with heFH in the parent study and have completed one of the four randomized, double-blind, 18-month parent studies. Patietns who missed the last injection or who perfromed the end of treatment visti outside the expected timelines can also be enrolled.

The end of treatment visit of the Double-Blind Treatment Period of the parent study corresponds to the visit 1 (Day 1) of the OLE study, except for the patients having participated in the LTS11717. These latter patients will have the opportunity to enter the OLE study, after they have completed the parent study, including the 8 week follow-up period. Patients who meet eligibility criteria at the visit 1 (Day 1) will receive a first SC injection of alirocumab on that day.

All patients will receive 75 mg Q2W at entry into the OLE, with the exception of patients from EFC12732 (ODYSSEY High-FH). These latter patients, who had a screening LDL-C *160 mg/dL in the parent study, will hence receive 150 mg Q2W at entry into the OLE, as in the parent study.

At entry in the OLE (at visit 1 on Day 1):
* All eligible patients from EFC12732 will get the alirocumab dose 150 mg at Day 1.
* All eligible patients from EFC12492, R727-CL-1112 and LTS11717 will get 75 mg alirocumab.

The first SC injection of alirocumab will be administered in the clinic (Day 1, Visit 1). Patients from the LTS11717 will have the possibility to perform a placebo self-injection training before the first alirocumab administration using an auto-injector on that same day (Day 1), as they used a different device (a prefilled syringe) in the parent study.

From Visit 1, patients have the option to self-administer or have the study drug injection administered by another designated person (such as spouse, relative, etc.).

From Day 1 (Visit 1) until Week 8 (first unblinded LDL-C value), neither the treatment received at the end of the double-blind treatment period in the parent study, nor the lipid parameters level, will be known by the Investigator, and by the patient, in order to prevent any potential blinding breaking of the parent clinical study. However, from Week 8 (Visit 3) in the OLE, the lipid values will be communicated to the investigator in real time.

From Week 12 (Visit 4), the Investigator will be responsible, based on his/her own judgment and the patients* LDL levels, to manage alirocumab dose (up-titration from 75 to 150 mg every 2 weeks, down-titration from 150 to 75 mg every 2 weeks or maintenance of the dose, will be possible).

Daily dose of statin or of other lipid-modifying therapy (LMT) (if applicable) can be modified based on the Investigator*s judgment throughout the study.

After Week 24 (visit 5), visits will be scheduled every 24 weeks (approximately 6 months) and a dispensation visit will be scheduled in between the 24 weeks visits interval. This dispensation visit will allow to supply IMP for the next 3 months, and will also allow to check the treatment compliance, the concomitant medications, and occurrence of any adverse event.

Patients should be on a stable diet (NCEP-ATPIII TLC diet or equivalent) throughout the entire study duration from visit 1 (V1) to the end of OLE treatment period (OLETP) (V17).

Intervention

Injection at site

Study burden and risks

Patient assessments in the OLE period
* Day 1 / Week 0 (End of treatment visit of the parent double-blind study = OLE Visit 1, except for the patients having participated in the LTS11717).
* Complete study visits: Patients will be assessed in the clinic at Weeks 4 (Visit 2), 8 (Visit 3), 12 (Visit 4), 24 (Visit 5), and then every 24 weeks until Visit 17, or early termination.
* IMP dispensing visits: Between Week 24 and Week 120, IMP dispensing visits will be scheduled in-between the clinic visits in order to allow for dispensing IMP; they will be done at Weeks 36 (Visit 6), week 60 (Visit 8), 84 (Visit 10) and 108 (Visit 12), week 132 (visit 14), week 156 (visit 16)

The risks associated with administration of alirocumab to humans are not fully known. Clinical and laboratory evaluations will be reviewed and monitored closely on an on-going basis.

Side effects of alirocumab: Every drug has side effects, and alirocumab has these as well. These effects may be mild, but can also be of a serious nature and in a few cases life threatening. However, not every person will experience these side effects.

The most common side effects reported with alirocumab (occurring in at least 1% of patients) include: injection site reactions (such as, but not limited to redness, pain, bruising, swelling) , itching and flu (upper respiratory symptoms). None occurred in more than 6% of the patients

During the study, there is a chance that your LDL cholesterol may go to very low levels; lower than what is usually seen with other medicines used to treat high cholesterol. The potential consequences of developing low LDL cholesterol are unknown. Theoretical concerns related to low LDL-C include: decrease of hormones, peripheral nerve (part of the nervous system outside of the brain and spinal cord) abnormalities, anemia (decreased of number of cells in the blood that carry oxygen in the body), bleeding in the brain, impairment of thinking or memory and vitamin deficiencies. It should be noted that these theoretical risks have not been confirmed with alirocumab in human studies of up to 18 months where these specific risks were carefully monitored. Potential side effects will be monitored very closely during the study.

In studies done in rats, findings were seen in the eyes of some animals. In a six month study, the finding was in the nerve of the eye. In most cases, this was thought to be caused by trauma to the eye that was the result of a study procedure. The meaning of this finding is not clear. However, if a similar finding occurs in people it could result in vision changes. In studies done in people treated for up to 18 months with alirocumab, no increased risk was confirmed in vision changes due to the nerve of the eye. The only observation related to eyes was regarding
cataracts (clouding of the normally clear lens of the eye). It should be noted that no difference
was observed in the frequency of cataract between patients treated with alirocumab and patients
who received placebo or another treatment. However, in patients treated with alirocumab who
achieved a very low LDLC level, cataracts were observed in 2.1% of these patients versus 0.6 %
of patients with a higher LDL-C level.

Other potential risks that have been linked to blocking PCSK9: a decrease in the immune defense, liver disease, colorectal cancer or increased susceptibility to hepatitis C virus infection; however, it should be noted that these potential risks have not been confirmed in human studies of up to 18 months with alirocumab.

Allergic reactions: Rare side effects (occurring in less than 1% of patients)

were noted in patients who received alirocumab including allergic reaction, eczema (skin inflammation), urticaria (wheals), and vasculitis (inflammation of the walls of blood vessels in the skin).

Sometimes, people have serious allergic reactions to drugs. A severe allergic reaction could be life-threatening and may result in death. Symptoms of allergic reactions include rash, difficulty breathing, and coughing, wheezing, sudden drop of blood pressure, swelling of the mouth, throat or eyes, seizures, flushing, a fast pulse, and sweating.

Since alirocumab is an investigational drug when taken alone or in combination with other medications, there may be other risks that are unknown. All drugs have potential risk of an allergic reaction, which, if not treated promptly, could become life-threatening. Other rare or unknown side effects could possibly occur, including life-threatening reactions or death.

During blood draws, the patient may have pain and/or bruising at the place on the arm arm where blood is taken. Blood clots may form and infections may occur, but these events are rare. If the patient feels faint, the patient should lie down right away to avoid falling down.

During this study, the patient may benefit from closer medical observation, dietetic follow-up, and study drug administration. In connection with these activities, cholesterol may improve.

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

* Eligible patients for this OLE study will be men and women diagnosed with heFH in the parent study and who have completed one of the following studies, EFC12492, R727-CL-1112, EFC12732 or LTS11717. Patietns who mised the last injection or who perfromed the end of treatment visti outside the expected timelines can also be enrolled.

Exclusion criteria

* Significant protocol deviation in the parent study based on the Investigator judgment, such as non-compliance by the patient.
* Adverse event leading to permanent discontinuation from parent study.
* Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.
* Positive pregnancy test at the end of treatment visit or end of study visit, according to the parent study the patient was originating from.
* Women of childbearing potential not willing to continue highly-effective method of birth control and/or who are unwilling or unable to be tested for pregnancy.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-02-2014
Enrollment:	163
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	alirocumab
Generic name:	nvt

Ethics review

Approved WMO Date:	18-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-12-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2015
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2013-002572-40-NL
Other	IND NUMMER 105574
CCMO	NL46219.018.13

Study results

Date completed:	23-01-2017
Actual enrolment:	133