Open-label, Single-arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH)

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PrimaryTo describe the safety and tolerability of 80 weeks of SC evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH. Secondary Efficacy* To describe percent change and change from baseline in LDL-...

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

Summary

ID

NL-OMON55627

Source
ToetsingOnline

Brief title
HAUSER-OLE

Condition

- Metabolic and nutritional disorders congenital

Synonym
HoFH, Hypercholesterolemia - HeFH

Research involving
Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: Evolocumab, Familial Hypercholesterolemia, Open label, Pediatrics

Outcome measures

Primary outcome

The primary clinical hypothesis is that SC evolocumab will be well tolerated

when added to standard of care in pediatric subjects 10 to 17 years of age with

HeFH or HoFH.

Primary Endpoint: Treatment emergent adverse events

Secondary outcome

Secondary Efficacy Endpoints:

* Percent change from baseline at week 80 in:

* LDL-C

* non-HDL-C

* ApoB

* total cholesterol/HDL-C ratio

* ApoB/ApoA1 ratio

* Change from baseline in LDL-C at week 80

Secondary Safety Endpoints:

* Change from baseline in steroid hormones (estradiol in females, testosterone in males; follicle-stimulating hormone [FSH], luteinizing hormone [LH], adenocorticotropic hormone [ACTH], dehydroepiandrosterone sulfate [DHEA-S], cortisol in all subjects) at week 80

* Abnormal muscle and liver enzyme levels (creatine kinase [CK], aspartate aminotransferase [AST], or alanine aminotransferase [ALT]) at week 80

* Change in cIMT from baseline at week 80

* Change from baseline in growth (height and weight) and pubertal development (Tanner staging) at weeks 24, 48, and 80

Study description

Background summary

Hypercholesterolemia (elevated serum low-density lipoprotein cholesterol [LDL-C]) is an established risk factor for coronary heart disease (CHD) in humans (Grundy et al, 2004), and more than 50 million patients are treated for hypercholesterolemia in the United States and Europe (Kuklina et al, 2011; Kotseva et al, 2009; Tolonen et al, 2005). Cholesterol elevations requiring pharmacologic therapy are uncommon in children. However, patients with familial hypercholesterolemia (FH), an almost exclusively autosomal dominant condition most often resulting from deficient or defective LDLR function (Rader et al, 2003), have elevated LDL-C beginning in childhood. Since FH is a genetic condition, the prevalence among children is very similar to the prevalence among younger adults.

In the pediatric population, FH may be identified by the combination of elevated LDL-C and a positive family history of hypercholesterolemia and/or premature cardiovascular disease. HeFH affects approximately one out of every 200 to 500 people worldwide (National Collaborating Centre, 2008; Nordestgaard

et al, 2013; Rader et al, 2003). By comparison, HoFH is present in approximately 1 in 1,000,000 individuals (Goldstein et al, 2001). Without treatment, these patients have severe hypercholesterolemia, develop premature coronary artery disease, and are at increased risk for premature cardiovascular death (Rader et al, 2003). Because premature atherosclerosis and especially coronary artery disease are part of the natural history of FH, events related to coronary artery disease and its complications (eg., manifestations of myocardial ischemia such as chest pain and myocardial infarction; percutaneous and surgical revascularization procedures, etc.) are expected to occur in this population at some frequency regardless of drug exposure.

In the adult population, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are currently the treatment of choice for patients with HeFH and HoFH patients (Grundy et al, 2004). Although statins reduce mortality in this patient population (Raal et al, 2011), cholesterol levels may remain elevated in FH patients despite therapy with diet, exercise, and medications. Pediatric guidelines in the United States (Daniels and Greer, 2008; McCrindle et al, 2007; Kavey et al, 2006) recommend considering pharmacologic treatment after initial treatment with lifestyle modification has failed in patients >= 10 years of age with LDL-C that is:
* >= 130 mg/dL (3.4 mmol/L) for the highest risk (eg, diabetes mellitus)
* >= 160 mg/dL (4.1 mmol/L) for intermediate risk (eg, >= 2 other CHD risk factors, family history of premature coronary artery disease [CAD])
* >= 190 mg/dL (4.9 mmol/L) for the lowest risk (no cardiovascular risk factors)

Similarly, treatment guidelines from the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS; Reiner et al, 2011) and from the National Institute for Health and Clinical Excellence (NICE; National Collaborating Centre, 2008) recommend statin treatment in patients who are >= 10 years of age and have HeFH or HoFH, and consider pharmacologic treatment for subjects with HoFH at earlier ages
(Reiner et al, 2011). When a child with FH has exceptionally high LDL-C and/or cardiovascular risk, bile acid sequestrants and ezetimibe are also indicated and may be used in combination. Thus, while currently available therapies can reduce LDL-C levels, novel therapies that can be used alone or in combination with existing agents to more effectively reduce LDL-C would be valuable for both adults and pediatric patients with severely elevated cholesterol levels.

Study objective

Primary
To describe the safety and tolerability of 80 weeks of SC evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH.

Secondary Efficacy
* To describe percent change and change from baseline in LDL-C, and on percent

change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, in pediatric subjects 10 to 17 years of age with HeFH or HoFH after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

Secondary Safety
* To describe change from baseline in steroid hormones and the subject incidence of abnormal muscle and liver enzyme levels after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
* To describe changes from baseline in carotid intima-media thickness (cIMT) after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
* To describe change from baseline in growth and pubertal development parameters at measured timepoints with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

Other Safety
* To evaluate the incidence of abnormal neurological examination findings after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
* To assess cognitive function, assessed using the change from baseline in the components of the Cogstate battery at each scheduled administration, after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH

Exploratory
* To describe change and percent change at measured timepoints in LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, lipoprotein(a) [Lp(a)], with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
* To describe change at measured timepoints in proprotein convertase subtilisin/kexin type 9 (PCSK9) and high sensitivity C-reactive protein (hsCRP) with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
* To describe the incidence of abnormal neurological examination findings with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
* To investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of evolocumab in pediatric subjects 10 to 17 years of age with HeFH
* In subjects consenting to the optional pharmacogenetics analysis, to investigate potential correlations of study data including the subject response to evolocumab with genetic variation in markers of (PCSK9) signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism,

inflammation, and plaque stability

Study design

This is an open-label, single-arm, multicenter study. Subjects are eligible for screening if they have completed Study 20120123 or if they are 10 to 17 years of age at time of enrollment and have HoFH. The minimum expected enrollment of HeFH (rollover) subjects is approximately 70% of subjects enrolled in Study 20120123 or approximately 111 subjects. In addition, approximately 10 subjects with HoFH (and without prior participation in an evolocumab study) will be enrolled for an expected total enrollment of approximately 124 subjects. Depending on willingness of 20120123 subjects to continue evolocumab administration, final enrollment may be smaller or greater. The study includes collection of biomarker development samples. Where permitted by local regulations, subjects will be invited to consent/assent to pharmacogenetic analyses

Intervention

The subjects will be enrolled to receive monthly Evolocumab for the period of 80 weeks, by means of 3 subcutane injections.

Study burden and risks

Patients will have more visits to the hospital; risks associated with participation are the one linked to the investigational product.

Contacts

Public
Amgen

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NL
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

All Subjects:
• Subject has provided written informed consent or subject assent prior to initiation of any study-specific activities/procedures.
and/or
• Subject*s legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written subject assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated.

Subjects with HeFH:
• Completed Study 20120123 while still on assigned investigational product.

Subjects with HoFH:
• Male or female, >= 10 to <= 17 years of age at time of enrollment (includes the year after the subject completes the 17th year after birth but not the day of completing the 18th year after birth).
• Diagnosis of HoFH by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL cholesterol 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.
• Subject must be on a low-fat diet and receiving background lipid-lowering therapy (such as statins, cholesterol absorption inhibitors, bile acid sequestrants, nicotinic acid, or combinations thereof).
• Lipid-lowering therapy, including statin dose, must be unchanged for >= 4 weeks prior to LDL-C screening; fibrates must be stable for at least 6 weeks prior to screening.
• Fasting LDL-C at screening >= 130 mg/dL (3.4 mmol/L) as determined by central

laboratory.
• Fasting triglycerides <= 400 mg/dL (4.5 mmol/L) by central laboratory at screening.

Exclusion criteria

All Subjects:
• Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s). Other investigational procedures or treatments while participating in this study are excluded.
• Female subject who has experienced menarche and unwilling to use acceptable method(s) of effective birth control during treatment with evolocumab and for an additional 15 weeks after the end of treatment with evolocumab. A female who has experienced menarche is considered of childbearing potential.
• Female subject is pregnant or breast feeding, or planning to become pregnant or planning to breastfeed during screening, during treatment with evolocumab, and within 15 weeks after the end of treatment with evolocumab.
• Unreliability as a study participant based on the investigator's (or designee*s) knowledge of the subject (eg, alcohol or other drug abuse in the past year, inability or unwillingness to adhere to the protocol, or psychosis).
• Subject will not be available for or likely not to comply with protocol-required study visits or procedures, to the best of the subject and investigator*s knowledge (Note: Day 1 and week 80 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation).
• Known sensitivity to any of the active substances or their excipients to be administered during dosing, eg, carboxymethylcellulose.

Subjects with HoFH:
• Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m2 at screening, confirmed by a repeat measurement at least 1 week apart. Note: eGFR will be calculated by the central laboratory and will be provided to the site for eligibility determination.
• Persistent active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the ULN as determined by central laboratory analysis at screening, confirmed by a repeat measurement at least 1 week apart.
• CK > 3 times the ULN at screening, confirmed by a repeat measurement at least 1 week apart.
• Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction in the judgment of the investigator.
• Subject has taken a cholesterylester transfer protein (CETP) inhibitor such as anacetrapib, dalcetrapib or evacetrapib in the last 12 months, or mipomersen or lomitapide in the last 5 months prior to LDL-C screening.

• Subject has received evolocumab or any other therapy to inhibit PCSK9 within 12 weeks of screening.
• History or evidence of any other clinically significant disorder, condition or disease, or planned or expected procedure that, in the opinion of the Investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

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):	20-04-2017
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Repatha
Generic name:	Evolocumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	22-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	11-04-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	09-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2021
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	EUCTR2015-002276-25-NL
ClinicalTrials.gov	NCT02624869
CCMO	NL56501.018.16

Study results