Double-blind, Randomized, Multicenter, Placebo-controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-cholesterol (LDL-C) Reduction, as Add-On to Diet and Lipid-Lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH)

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To evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab compared with placebo, when added to standard of care, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in pediatric subjects 10 to 17 years of age with...

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

Summary

ID

NL-OMON47734

Source
ToetsingOnline

Brief title
20120123 - HAUSER-RCT

Condition

- Metabolic and nutritional disorders congenital

Synonym
Hypercholesterolemia in children - HeFH

Research involving
Human

Sponsors and support

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

Intervention

Keyword: double-blind, Evolocumab, Familial Hypercholesterolemia, Pediatrics

Outcome measures

Primary outcome

Hypotheses: The primary hypothesis is that SC evolocumab will be well tolerated and will result in greater reduction of LDL-C, defined as percent change from baseline to week 24, compared with placebo, when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH.

Primary Endpoint: Percent change from baseline to week 24 in LDL-C

Secondary outcome

Secondary Endpoints:

• Mean percent change from baseline to weeks 22 and 24 in LDL-C

• change from baseline to week 24 in LDL-C

• percent change from baseline to week 24 in the following:

* non-HDL-C

* ApoB

* total cholesterol/HDL-C ratio

* ApoB/ApoA1 ratio

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). In the adult population, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are currently the treatment of choice for both heterozygous FH patients and homozygous FH patients (Grundy et al, 2004), as statins inhibit endogenous cholesterol biosynthesis and upregulate LDLR expression (increasing the activity of functional LDLR) (Rader et al, 2003). 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

To evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab compared with placebo, when added to standard of care, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in pediatric subjects 10 to 17 years of age with HeFH.

Study design

This is a randomized, multicenter, placebo-controlled, double-blind, parallel group study. Subjects are eligible for screening if they are 10 to 17 years of age at time of randomization and have met the local applicable diagnostic criteria for HeFH. Subjects considered for enrollment will undergo screening assessments, including laboratory screening by central laboratory.
Approximately 150 eligible subjects will be randomized in a 2:1 ratio to receive 24 weeks of QM evolocumab or placebo. Randomization will be stratified by screening LDL-C (< 160 mg/dL [4.1 mmol/L] vs >= 160 mg/dL) and age (< 14 years vs >= 14 years).
The study includes collection of biomarker development samples. Where permitted by local regulations, subjects will be invited to consent to pharmacogenetic analyses.
After completion of Study 20120123, subjects will be offered to participate in an extension study where they will receive open-label evolocumab.

Intervention

Subjects being considered for participation in this study, and who have signed informed consent or subject assent, will be assessed for inclusion and exclusion criteria. Medical and medication history will be obtained. Subjects will undergo screening assessments, including a SC administration of placebo to evaluate tolerability of the SC injection via the prefilled AI/pen. Lipid eligibility screening must be conducted after the subject has been on a low-fat diet and receiving lipid lowering therapy that includes an optimal dose of a

statin not requiring uptitration in the opinion of the investigator and has been stable for >= 4 weeks. Subjects should maintain their diet, lipid-lowering therapy, and exercise regimen unchanged throughout screening and all phases of study participation. Eligible subjects will be randomized to receive IP (evolocumab or
placebo), in addition to their background lipid lowering therapy. An interactive voice response system and/or interactive web response system (IVRS/IWRS) will allocate subjects to administration of investigational product. Day 1 is defined as the day of first administration of investigational product. Subsequent study visits are at weeks 4, 12, 20, 22, and 24 (EOS, end-of-study). Day 1 and week 24 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. IP administration is every 4 weeks. Administration at weeks 8 and 16 can be at the study site (optional visit) or at a location other than the study site. Last administration of IP is at week 20. Subjects who discontinue IP early for any reason will be asked to continue to return for all other study procedures and measurements until the end of the study. Assessments and procedures include vital signs, adverse events/serious adverse events/adverse device effects (ADE)/disease related events(DRE)/cardiovascular (CV) events, and concomitant therapy, dietary instruction, physical exam including neurologic examination and assessment of waist circumference, body height and weight, 12-lead electrocardiograms (ECGs), fasting lipids, chemistry, hematology, anti-evolocumab antibodies, biomarker sample collection, serum pregnancy testing (females of childbearing potential), urinalysis, assessment of growth and pubertal development (Tanner staging), Cogstate neurocognitive assessment, carotid intima-media thickness (cIMT), and IP administration. In
addition, specific laboratory assessments will be performed, including estradiol for girls, testosterone for boys, creatinine phosphokinase, follicle-stimulating hormone, luteinizing hormone, adenocorticotropic hormone, dehydroepiandrosterone, and cortisol. If the subject consented to pharmacogenetics analyses, DNA will be extracted from some of the blood samples. IP administration by SC injection, if applicable, will be done after all other procedures have been completed.

Study burden and risks

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

Contacts

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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

- Male or female, aged 10 to 17 years of age at time of randomization
- Diagnosis of heterozygous familial hypercholesterolemia by local applicable diagnostic criteria for HeFH or by genetic testing.
- Subject must be on an approved statin with stable dose for >= 4 weeks before LDL*C screening and, in the opinion of the investigator, not requiring up*titration
- Fasting LDL-C at screening >= 130 mg/dL (3.4 mmol/L)
- Subject has fasting triglycerides <= 400 mg/dL (4.5 mmol/L)

Exclusion criteria

- Type 1 diabetes, newly diagnosed/ poorly controlled type 2 diabetes (HbA1c>8,5%), or newly diagnosed impaired glucose tolerance.
- Untreated or inadequately treated hyper/hypo-thyroidism

- Moderate to severe renal dysfunction (eGFR < 30 ml/min/1.73m2 at screening)
- Persistent active liver disease or hepatic dysfunction (AST or ALT >2 times ULN as determined by central lab analysis at screening)
- 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

Study design

Design

Study phase:	3
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):	01-11-2016
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Repatha
Generic name:	Evolocumab

Ethics review

Approved WMO

Date:	24-02-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-09-2017
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:	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:	09-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2018
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:	10-02-2020
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	EUCTR2014-002277-11-NL
ClinicalTrials.gov	NCT02392559
CCMO	NL52822.018.16