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Efficacy, safety, and tolerability of evolocumab in pediatric patients with heterozygous familial hypercholesterolemia: Rationale and design of the HAUSER-RCT study

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Monoclonal antibody;
Safety

BACKGROUND: Evolocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, is safe and effective in reducing low-density lipoprotein cholesterol in adults with familial hypercholesterolemia. A dedicated study, HAUSER-RCT, is being conducted to examine the efficacy and safety of evolocumab in pediatric patients with heterozygous familial hypercholesterolemia (HeFH).

OBJECTIVE: To present the rationale and design of the HAUSER-RCT study.

METHODS: The HAUSER-RCT study is a double-blind, randomized, multicenter, placebo-controlled study designed to characterize the efficacy, safety, and tolerability of evolocumab treatment as an add-on to diet and lipid-lowering therapy, including a stable, optimized dose of statin, in pediatric patients aged 10 to 17 years with HeFH. Approximately, 150 patients will be randomized in a 2:1 ratio to receive 24 weeks of monthly evolocumab or placebo. The study will include approximately 51 sites located in North America, South America, Europe, South Africa, Australia, and New Zealand. The primary efficacy endpoint is the percent change in low-density lipoprotein cholesterol from baseline to week 24. A key secondary efficacy endpoint is the percent change in other lipid parameters from baseline to week 24. Other assessments include Tanner staging, carotid intima-media thickness, and cognitive tests. At the end of the study, consenting patients can participate in an 18-month open-label extension study (HAUSER-OLE).

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RESULTS: The study is ongoing and the results will be communicated at the end of the study.
CONCLUSIONS: The HAUSER-RCT study, the largest randomized, placebo-controlled study with proprotein convertase subtilisin/kexin type 9 inhibitors being conducted in the pediatric HeFH population, aims to provide efficacy, safety, and tolerability data of evolocumab as an add-on therapy in these patients.

Introduction

Low-density lipoprotein cholesterol (LDL-C) plays a major role in the initiation and progression of atherosclerotic cardiovascular disease (ASCVD).[1] Familial hypercholesterolemia (FH) is caused by mutations in genes encoding proteins that regulate LDL receptor (LDLR)-mediated clearance of LDL-C. These include the genes for *LDLR*, apolipoprotein B (*APOB*), proprotein convertase subtilisin/kexin type 9 (PCSK9), and LDLR adaptor protein 1.[2,3] The prevalence of the heterozygous form of FH (HeFH) has been estimated to be approximately 1 in 200-250 persons in the general population.[4] FH is the most common inherited cause of premature ASCVD and growing evidence suggests that the development of atherosclerosis in patients with FH begins early in life, even in childhood.[2,3,5] Children with untreated FH have an increased risk of premature ASCVD in adulthood,[2,3] and it is acknowledged that early treatment to lower LDL-C levels can reduce the ASCVD risk burden that FH imposes.[5]

Statins are the backbone of FH management in adults and children. Current guidelines for lipid lowering in children recommend statins as the first-line treatment.[5–7] Several studies have shown that statins reduce LDL-C in children and adolescents with FH.[5] The PLUTO study demonstrated safe and effective reduction of LDL-C in FH pediatric patients but highlighted how difficult it is to achieve LDL-C goals for preventing cardiovascular disease.[8] Increased carotid intima-media thickness (cIMT), an indicator of the onset of subclinical atherosclerosis, has been found in children with untreated FH, before the age of 8–10 years, compared with unaffected siblings.[9–11] In a study conducted in children with HeFH in the Netherlands, treatment with a statin induced a significant regression of cIMT,[11] regarded as a sign of early atherosclerosis.[12] In the more recent CHARON study, children with HeFH aged 6 years and older treated with statins daily showed significant LDL-C reduction and slowing of cIMT progression and normalization of cIMT at 2 years, compared with untreated, unaffected siblings.[13,14]

Evolocumab is a fully human monoclonal antibody that lowers LDL-C by binding to PCSK9 and inhibiting PCSK9-mediated degradation of LDLR.[15,16] Evolocumab is currently approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of hypercholesterolemia (HeFH and nonfamilial), mixed dyslipidemia, and homozygous FH (HoFH). In the recent Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER [NCT01764633]) study, 27,564 adults with clinically evident cardiovascular disease and high-risk characteristics were randomized to receive either evolocumab or placebo. With a median follow-up of 26 months, evolocumab treatment reduced LDL-C from a median baseline value of 2.4 mmol/L (92 mg/dL) to 0.78 mmol/L (30 mg/dL), $P < .001$, and reduced the risk of cardiovascular events.[17] The potential effect of evolocumab on cognitive function was investigated in over 1900 Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk patients who enrolled in the Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS [NCT02207634]) study. With a median study exposure of approximately 19 months in Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects, cognitive function was not affected with the addition of evolocumab to statin therapy, even for patients who achieved an LDL-C level of <0.6 mmol/L (25 mg/dL).[18]

Current information regarding the efficacy and safety of evolocumab in the pediatric population comes exclusively from patients with HoFH. The Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities (TESLA [NCT01588496]) study was a phase 2/3 randomized, placebo-controlled study evaluating the efficacy and safety of evolocumab in 57 HoFH patients aged ≥12 years, including 11 patients younger than 18 years, 8 of whom received evolocumab.[19,20] The Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects With Genetic LDL Disorders (TAUSSIG [NCT01624142]) study is an ongoing, phase 2/3, multicenter, open-label study of evolocumab in 300 patients with HoFH or severe HeFH aged ≥12 years. Of these 300 patients, 106 have HoFH, including 14 patients younger than 18 years at the time of enrollment.[21]

The HAUSER-RCT study will provide additional data to the existing efficacy and safety data of evolocumab in a larger population of pediatric patients with HeFH. The HAUSER-RCT open-label extension study (HAUSER-OLE) will provide long-term efficacy and safety data of evolocumab in this pediatric population.

Methods

Study design

The HAUSER-RCT (NCT02392559) study is an ongoing, phase 3, randomized, placebo-controlled, double-blind,

parallel-group, multicenter study designed to assess the efficacy, safety, and tolerability of evolocumab in pediatric patients aged 10 to 17 years with HeFH. HAUSER-RCT will include approximately 51 sites from 20 countries in North America, South America, Europe, Africa (South Africa), and Oceania (Australia and New Zealand) (Fig. 1). The first patient enrolled in March 2016. In the study, patients are randomized in a 2:1 ratio to receive 24 weeks of evolocumab once monthly (QM) or matching placebo (Fig. 2). Randomization is stratified by screening LDL-C (<4.1 mmol/L [160 mg/dL] vs ≥ 4.1 mmol/L) and age (<14 years vs ≥ 14 years). Patients completing the HAUSER-RCT will be eligible to enter the 18-month HAUSER-OLE study. All procedures in this study are conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. The Ethics Committees and Institutional Review Boards of each site reviewed and approved the final protocol and informed consent forms.

Study objectives and endpoints

The primary objective of the HAUSER-RCT study is to evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab compared with placebo, when added to optimized statin therapy, on percent change from baseline in LDL-C. Secondary objectives include evaluation of the safety of SC evolocumab compared with placebo, when added to optimized statin therapy; mean percent change from baseline to weeks 22 and 24 and change from baseline to week 24 in LDL-C; and percent change from baseline to week 24 in nonhigh-density lipoprotein cholesterol (non–HDL-C), ApoB, total cholesterol/HDL-C ratio, and ApoB/apolipoprotein A1 (ApoA1) ratio. Tertiary objectives include assessment of the effects of SC evolocumab compared with placebo, when added to standard of care, on percent change from baseline to week 24 in total cholesterol, very low-density lipoprotein cholesterol, HDL-C, ApoA1, triglycerides, and lipoprotein(a); and on mean percent change from baseline to weeks 22 and 24 in non–HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, total cholesterol, very low-density lipoprotein cholesterol, HDL-C, ApoA1, and triglycerides.

The primary endpoint of HAUSER-RCT is percent change from baseline to week 24 in LDL-C. Patient incidence of adverse events is a secondary safety endpoint. Additional study endpoints are shown in Table 1.

Study hypothesis

The primary hypothesis of the HAUSER-RCT study 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, than placebo when added to diet and lipid-lowering therapy, including a stable, optimized dose of statin, in pediatric patients aged 10 to 17 years with HeFH.

Study population

Patients are eligible if they are aged 10 to 17 years at the time of randomization and meet the local applicable diagnostic criteria for HeFH as described in Table 2. Briefly, patients are being assessed for HeFH by genetic testing or clinically by one of several criteria: Simon

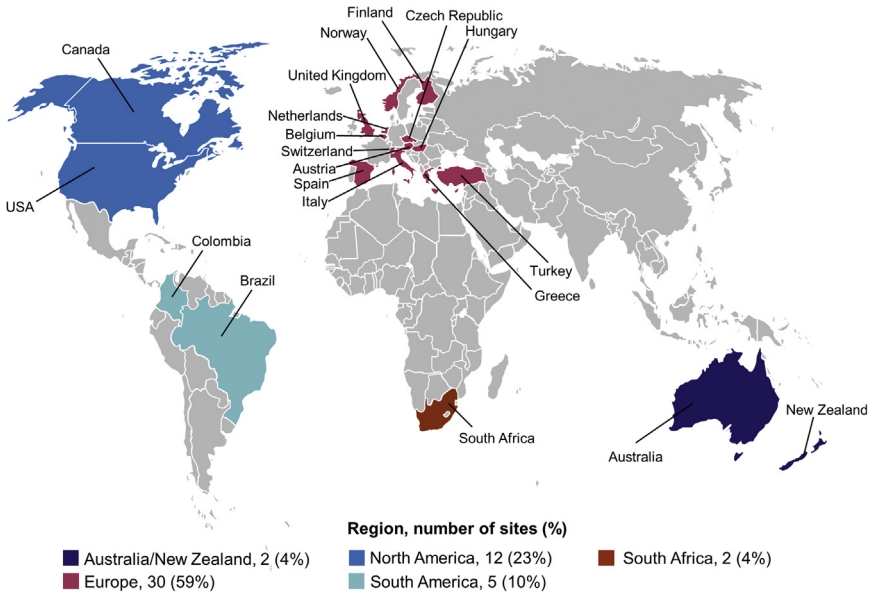

Figure 1 HAUSER-RCT study sites. Countries that house study sites are depicted in the map. The legend shows the number and percentage of study sites by region.

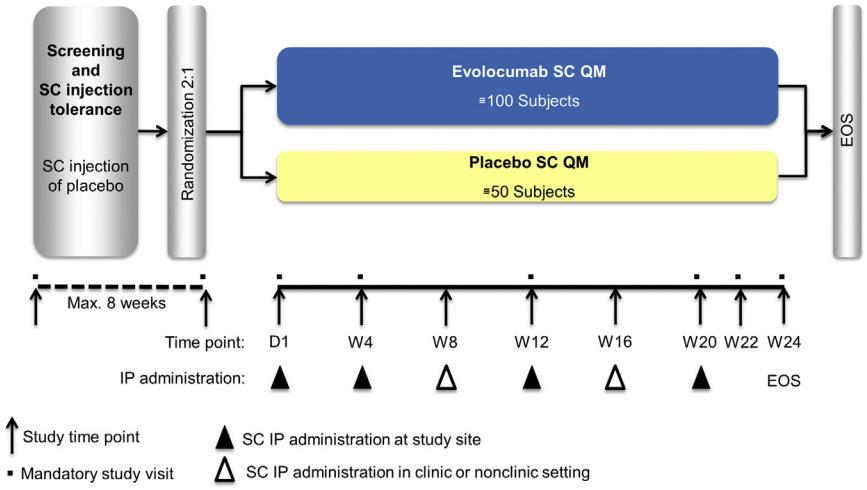

Figure 2 Study design and treatment schema. Patients considered for enrollment undergo screening assessments, including laboratory screening by a central laboratory. Approximately 150 eligible patients are randomized in a 2:1 ratio to receive 24 weeks of QM evolocumab or placebo. Randomization is stratified by screening low-density lipoprotein cholesterol (<4.1 mmol/L [160 mg/dL] vs ≥ 4.1 mmol/L) and age (<14 years vs ≥ 14 years). D, day; EOS, end of study; IP, investigational product; QM, once monthly; SC, subcutaneous; W, week.

Broome Register Group, Dutch Lipid Clinic Network, or MEDPED. Only if parental/guardian consent or permission and subject consent or assent to optional pharmacogenetics analyses has been provided, DNA analyses may be performed. Furthermore, pharmacogenetic assessment can only be performed according to country-specific regulations when allowed. Although genetic testing is not a requirement, currently most patients in the study are undergoing genetic testing. Patients must be on a low-fat diet, have received an approved statin with stable dose for ≥4 weeks before LDL-C screening, and have fasting lipid concentrations of ≥3.4 mmol/L (130 mg/dL) for LDL-C and ≤4.5 mmol/L (400 mg/dL) for triglycerides. Although current European guidelines recommend starting statin treatment in patients with FH between the ages of 8 to 10 years,[25] the minimum age of enrollment of 10 years was selected for the HAUSER-RCT study to ensure that a global disparity in enrollment did not occur, as current guidelines in the United States recommend a minimum age of 10 years to start treatment with statins.[7] If patients are on any other lipid-lowering therapy, including ezetimibe, the therapy has to be unchanged for ≥4 weeks before LDL-C screening, with the exception of fibrates, which have to be stable for at least 6 weeks before screening. Patients are excluded if they have undergone lipid apheresis within the last 12 weeks before screening. Additional inclusion and exclusion criteria are shown in Table 2.

Table 1 Study endpoints

Endpoint	Description
Primary	• Percent change from baseline to week 24 in LDL-C
Secondary efficacy	• 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 non–HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio
Secondary safety	• Patient incidence of adverse events • Safety laboratory values and vital signs at each scheduled assessment • Incidence of antievolocumab antibody (binding and neutralizing) formation
Secondary pharmacokinetic	• Serum concentration of evolocumab at each scheduled assessment
Tertiary efficacy	• Percent change from baseline to week 24 in total cholesterol, VLDL-C, HDL-C, ApoA1, triglycerides, and Lp(a) • Mean percent change from baseline to weeks 22 and 24 in non–HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, total cholesterol, VLDL-C, HDL-C, ApoA1, triglycerides, and Lp(a)
Other safety	• Change from baseline score in the components of the Cogstate battery at each scheduled administration

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low–density lipoprotein cholesterol.

Study procedures

Informed consent

All patients and/or parents/legally acceptable representatives must sign and date the informed consent form or patient assent form before commencement of any study-specific activities/procedures.

Investigational product

Each dose of blinded investigational product (evolocumab QM or matching placebo) is administered SC via prefilled autoinjector. During screening and before enrollment, all patients receive a placebo injection to confirm tolerance to the injection. At weeks 8 and 16, patients are given the option to administer investigational product at home (ie, self-administration or administration by a parent or caregiver). All other scheduled doses (day 1, week 4, week 12, and week 20) are administered at the study site.

General assessments

At baseline, demographic data, medical history, and medications that the patients receive are recorded, and instruction for a low-fat diet is given. At the beginning and end of the study, all patients undergo physical examination including a neurologic examination and measurement of body height, weight, and waist circumference. A 12-lead electrocardiogram is obtained at baseline, week 12, and the end of the study. At each scheduled visit, vital signs are measured, and review for adverse events and any changes in medications is performed.

Laboratory assessments

At baseline, TSH is measured to exclude uncontrolled thyroid disease. Fasting lipids, evolocumab levels, and PCSK9 levels are assessed at baseline, week 12, week 22, and at the end of the study. Complete blood count, chemistry panel including liver function tests and fasting glucose, anti-evolocumab antibodies, urinalysis with urine microalbumin, and pregnancy testing (in female patients of childbearing potential) are performed at baseline, week 12, and the end of the study. Hemoglobin A1c, high-sensitivity C-reactive protein, creatine kinase, and fat-soluble vitamins (A, D, E, and K) are measured at baseline and the end of the study.

Specific tests

Specific tests are conducted at baseline and week 24 as safety measures to assess the cognitive function, pubertal growth and development, and atherosclerosis progression in the pediatric patients.

Cogstate battery

Cognition is assessed with the Cogstate cognitive battery (Cogstate Ltd, Australia) at the beginning and end of the study. The tests and corresponding cognitive domains in the battery are the Groton Maze Learning Task (executive function), One Card Learning Test (visual memory), Identification Test (attention/vigilance), and Detection Test (psychomotor speed).[26] Details of the Cogstate tests are in the Appendix.

Assessment of pubertal development

Tanner stage is assessed at the beginning and end of the study. Estradiol (girls), testosterone (boys), follicle-stimulating hormone, luteinizing hormone, adrenocorticotropic hormone, dehydroepiandrosterone, and cortisol are measured at the beginning and end of the study as well.

cIMT

cIMT is measured by B-mode ultrasound scanning at the beginning and end of the study. The cIMT images include longitudinal plane views in the anterior, lateral, and posterior imaging angles of each common carotid artery (containing the carotid bulb and the distal 10 mm segment of the right and left common carotid artery). The images include a 3–5 beat cine loop and an optimized end-diastolic still frame for each imagining angle. The cIMT images are read by a central laboratory.

Statistical design and analysis

Conservatively assuming a treatment effect of a 40% reduction in LDL-C, a planned total sample size of 150 patients (100 randomized to evolocumab QM and 50 to placebo QM), will provide approximately 99% power in testing the superiority of evolocumab QM over placebo. The sample size calculation was performed using a 2-sided *t*-test with a 0.05 significance level, assuming a treatment effect of 40% reduction in LDL-C, a common standard deviation of 20%, and 20% of patients discontinuing investigational product before completion of the study.

Efficacy and safety analyses will be performed on all randomized patients who have received at least 1 dose of the investigational product. Repeated-measures linear mixed-effects models will be used to assess the primary endpoint of percent change from baseline in LDL-C at week 24 as well as the secondary and tertiary efficacy endpoints. Models will include terms for treatment group, stratification factors, scheduled visit, and the interaction of treatment with the scheduled visit. Multiplicity adjustment for the multiple endpoints will be performed using sequential gatekeeping and Hochberg procedures[27] to preserve the familywise error rate at 0.05.

Safety summaries will include the patient incidence of adverse events, summaries of laboratory parameters, vital signs, and antievolocumab antibodies (binding and neutralizing). cIMT will be summarized at scheduled visits by the treatment group. Tanner stage will be summarized by the treatment group and gender.

Study organization

An independent data monitoring committee reviews the accumulating data from this and other completed and ongoing studies with evolocumab to ensure that there is no avoidable increased risk of harm to patients. An

Table 2 Eligibility criteria

Criteria	Description
Inclusion	• Signed informed consent • Male or female patients ≥10 to ≤17 y of age • Diagnosis of heterozygous FH: – Genetic testing, or Simon Broome Register Group,[22] Dutch Lipid Clinic Network,[23] or MEDPED[24] criteria • On approved statin with stable dose for ≥4 wk before screening • On a low-fat diet • If other lipid-lowering therapy, examples include: – Ezetimibe, bile-acid sequestering resin, omega 3 fatty acids, or niacin (stable for ≥4 wk before screening) – Fibrates (stable for ≥6 wk before screening) • Fasting LDL-C at screening ≥3.4 mmol/L (130 mg/dL) • Fasting triglycerides at screening ≤4.5 mmol/L (400 mg/dL)
Exclusion	• Homozygous FH • Lipid apheresis within the last 12 wk before screening • Diabetes, including: – Type 1 diabetes – Newly diagnosed (within 3 mo of randomization) type 2 diabetes – Poorly controlled type 2 diabetes (HbA1c > 8.5%) – Newly diagnosed impaired glucose tolerance (within 3 mo of randomization) • Laboratory test (at screening): – TSH < LLN or > 1.5 × ULN – Free thyroxine levels are outside normal range – eGFR < 30 mL/min/1.73 m^2 – AST or ALT > 2 × ULN – CK > 3 × ULN • Known illness – Active infection – Major hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction per the judgment of the investigator – History or evidence of any other clinically significant condition or planned or expected procedure that, in the opinion of the Investigator or Amgen physician, would pose a risk to patient safety or interfere with the study • Medications – CETP inhibitor (last 12 mo before screening) – Mipomersen or lomitapide (last 5 mo before screening) – Evolocumab or any other investigational therapy to inhibit PCSK9 (any time) – Any current treatment in another investigational device or drug study, less than 30 d since ending treatment on another investigational device or drug study(s) • Other – Unavailability for protocol-required study visits or procedures – Unreliability as a study participant – Pregnancy, breastfeeding, or inadequate birth control in premenopausal female patients – Known sensitivity to any of the active substances or their excipients administered during dosing

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CETP, cholesteryl ester transfer protein; CK, creatine kinase; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolemia; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; LLN, lower limit of normal; PCSK9, proprotein convertase subtilisin/kexin type 9; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

independent clinical events committee adjudicates death by any causes, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure.

Discussion

To our knowledge, HAUSER-RCT is currently the largest global, randomized, placebo-controlled study with PCSK9 inhibitors in the pediatric population that will provide efficacy, safety, and tolerability data of evolocumab in HeFH pediatric patients. Longer-term efficacy, safety, and tolerability data of evolocumab in this patient population will be provided by the HAUSER-OLE study.

Intima-media thickening, one of the first signs of atherosclerosis, is detectable in children aged 6 to 10 years affected with FH when these children are compared to their unaffected siblings.[9] Although early treatment is recommended, the

appropriate intensity of treatment remains unknown.[5] The two goals of achieving a 50% reduction of LDL-C and LDL-C <3.4 mmol/L (130 mg/dL) have been advocated.[5,6] These goals and the recommended age of 8 to 10 years for initiation of drug therapy are based on expert opinion that takes into account results from several statin studies. Some children are not able to achieve LDL-C <3.4 mmol/L with the standard treatment of moderate-intensity stain alone or in combination with ezetimibe.[8,11,14,28–31] It has been hypothesized that additional lipid-lowering therapy to achieve even lower LDL-C levels may sufficiently regress atherosclerosis to allow for intermittent treatment rather than continuous treatment over the lifespan of a patient.[32] This is particularly important for women who may become pregnant or in other settings where treatments are not as readily available.

Several specific safety assessments are conducted to assess cognitive function, pubertal growth and development, and signs of atherosclerotic progression in the patients participating in HAUSER-RCT. Each of these assessments has been selected on the basis of specific rationale and will be performed at baseline and at the end of the study.

Cognitive function—Cogstate battery

The US Food and Drug Administration has been investigating reports of cognitive impairment associated with the use of lipid-lowering medications for several years.[33] Although the Food and Drug Administration did not identify an association between statins and cognitive impairment in their communications regarding adverse events and data from clinical studies and observational studies, a safety label advisory was mandated in 2012 for statin medications to note potential cognitive adverse events.[34] The Cogstate battery of tests was selected to assess cognitive function in HAUSER-RCT because the complexity of the exams is suitable for pediatric patients aged 10 to 17 years, and a normative data set representing data from a healthy population of patients in this age range is available for comparison.[26]

Pubertal growth and development—Tanner staging

The inclusion of Tanner staging and hormone levels was deemed appropriate as part of the safety evaluation as they had been first used as safety assessments in the DISC study,[35] a randomized controlled study of dietary intervention to lower cholesterol in children and subsequently in several randomized controlled studies with statin treatment in the pediatric population.[8,11,14,28–31] HAUSER-RCT will provide descriptive statistics for change from baseline for hormone levels and shift from baseline in Tanner staging that will be classified by study cohort, gender, and parent study treatment for patients continuing in the HAUSER-OLE study.

Atherosclerotic progression—cIMT

Children affected with FH have functional and structural abnormalities in their arteries that are indicative of accelerated preclinical atherosclerosis.[36] Risk factors identified in prepubertal children with FH, including increased LDL-C concentrations, contribute to diffuse thickening of the intima-media space.[10,37,38] Findings from the Young Finns study suggest that exposure to cardiovascular risk factors early in life potentially induces changes in arteries that contribute to the development of atherosclerosis.[39] The Bogalusa Heart study demonstrated that measurements of LDL-C and body mass index in children can predict cIMT in young adults.[40] Taking these factors into account, measurement of cIMT was included as a safety assessment in HAUSER-RCT, and cIMT measurements will also be included in the HAUSER-OLE. Of note, it has been shown that statins induce significant regression of cIMT in children with HeFH.[11,13] In HAUSER-RCT, baseline cIMT is measured while patients are receiving background lipid-lowering therapy, including a stable dose of statin. Any changes in cIMT during the course of this study should be attributed to the combined effect of evolocumab treatment on top of background lipid-lowering therapy.

Data from HAUSER-RCT may support placement of PCSK9 inhibitors in the treatment algorithm as an additional treatment option for pediatric patients who do not attain the treatment goal of LDL-C < 3.4 mmol/L with diet and lifestyle, statins, and ezetimibe or for patients who cannot tolerate an effective dose of statins or statins in combination with other lipid-lowering therapy.

Conclusion

Once completed, HAUSER-RCT and its associated open-label extension, HAUSER-OLE, will be the largest and longest-term clinical studies conducted in the pediatric FH population with a PCSK9 inhibitor. This study aims to provide accurate data on efficacy and safety of LDL-C management with evolocumab as add-on therapy in pediatric HeFH patients and help define the role of evolocumab in the treatment of this at-high-risk patient population.

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Supplementary data

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