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Original Article

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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Evolocumab;
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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).

Clinical Trial Registration URL: https://www.clinicaltrials.gov/. Unique identifier: NCT02392559.

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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,