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Impact of Evinacumab on coronary plaques in patients with Homozygous Familial Hypercholesterolemia: Protocol of the "EVOLVE-HoFH" study (EValuation of atherOma pLaque Volume after Evinacumab in HOmozygous Familial Hypercholesterolemia)

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ABSTRACT

Keywords
Homozygous Familial Hypercholesterolemia; Evinacumab; Coronary Computed Tomography Angiography (CCTA); Atherosclerosis; Plaque Regression; Observational Study; Rare Disease

Background: Homozygous Familial Hypercholesterolemia (HoFH) is a rare and severe genetic disorder characterized by markedly elevated low-density lipoprotein-cholesterol (LDL-C) levels from birth onwards, leading to accelerated and premature atherosclerotic cardiovascular disease (ASCVD). Evinacumab, a monoclonal antibody targeting angiopoietin-like protein 3 (ANGPTL3), has been shown to effectively reduce LDL-C in this population. However, its direct impact on coronary atherosclerotic plaque burden remains to be established. Given the rarity of the condition, randomized placebo-controlled clinical trials on major adverse cardiovascular events (MACE) are unfeasible.

Aim and Methods: This document describes the methodology of the EVOLVE-HoFH study, a real-world, observational, multicenter, international study (prospective and retrospective) designed to assess whether intensification of lipid-lowering therapy (LLT) with Evinacumab leads to regression or stabilization of the coronary atherosclerotic plaque burden as well as altered composition in patients with HoFH. The study will use Coronary Computed Tomography Angiography (CCTA), a validated surrogate risk marker, to compare changes in plaque volume in a group of patients initiating treatment with Evinacumab ("intensified treatment group") with a "conventional treatment comparator group." The primary endpoint is the difference in change in percent non-calcified plaque volume (%NCPV), a key indicator of plaque instability, between baseline and 18-24 months follow-up.

Conclusion: This pragmatic methodological approach is designed to overcome the barriers of research in rare diseases, allowing for the evaluation of a clinically relevant and mechanistically informative surrogate efficacy endpoint. The results will provide the first evidence of the beneficial impact of Evinacumab on coronary atherosclerosis, filling an important knowledge gap.

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Introduction

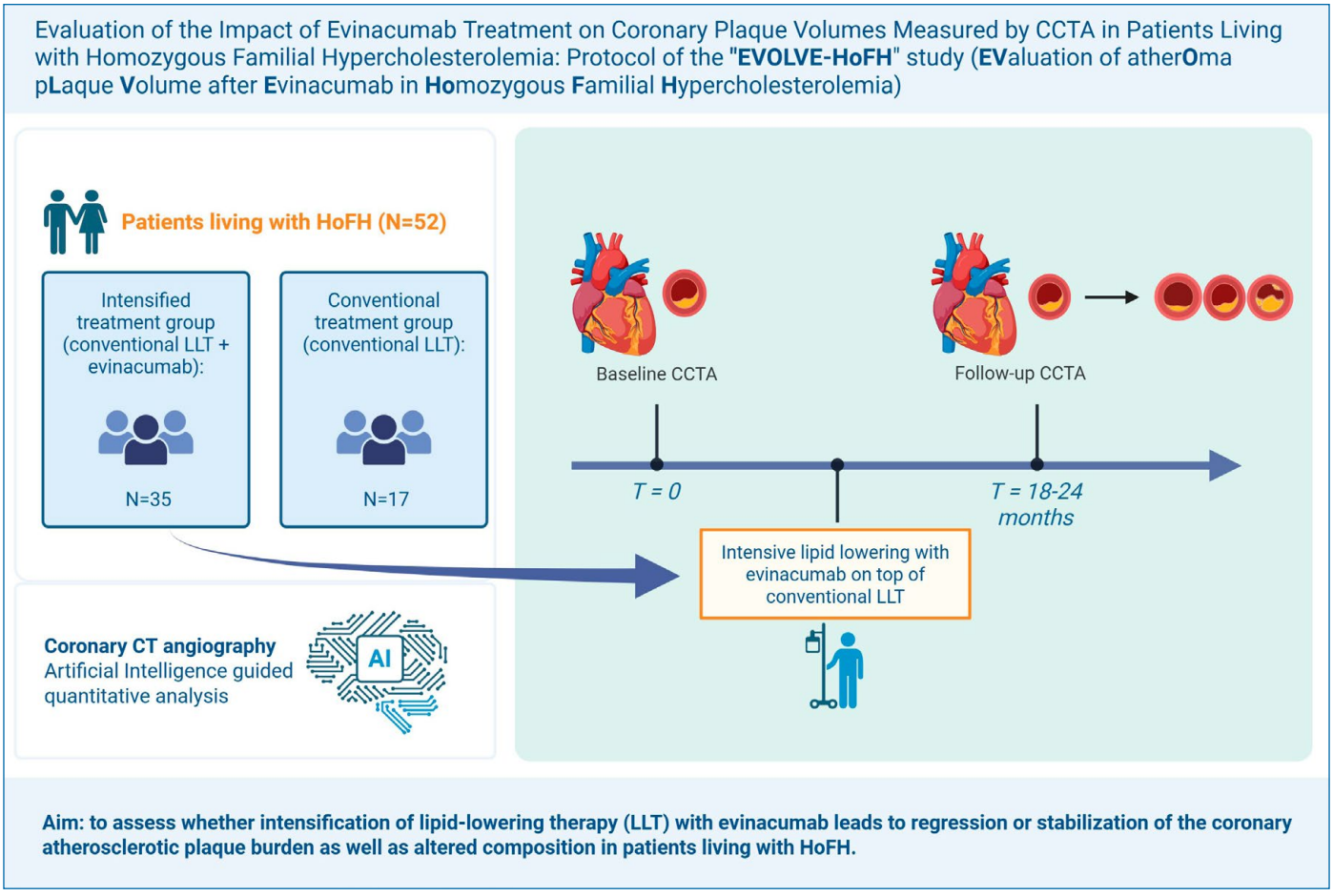
Homozygous Familial Hypercholesterolemia (HoFH) is a rare, life-threatening genetic disorder caused by bi-allelic mutations that result in near-complete or complete loss of low-density lipoprotein receptor (LDLR) function. This elicits lifelong exposure to extremely elevated LDL cholesterol (LDL-C) levels from birth, often exceeding 13 mmol/L (500 mg/dL) [1]. As a result, patients develop widespread and severe atherosclerosis, placing them at exceptionally high risk of premature cardiovascular events such as myocardial infarction and sudden cardiac death, often already in the second or third decade of life [2, 3].

Managing HoFH presents a major clinical challenge. Conventional lipid-lowering therapies (LLTs), including statins and ezetimibe, act primarily by upregulating hepatic LDLR activity. However, in individuals with HoFH – where LDLR function is severely impaired or absent – these therapies typically yield only modest LDL-C reductions. As such, standard pharmacological approaches are often insufficient to achieve the substantial LDL-C lowering needed to reduce cardiovascular risk in this high-risk population [3].

For many years, the escape treatment for refractory elevated LDL-C levels in HoFH revolved around lipoprotein apheresis (LA); an invasive, extracorporeal procedure analogous to dialysis. It involves filtering the blood outside the body to remove LDL-C before returning the filtered blood to the patient. While LA is effective in reducing LDL-C, it is also associated with considerable drawbacks. The procedure is costly, requiring specialized equipment and trained medical personnel. It is burdensome for patients, as it typically necessitates weekly or bi-weekly visits to a hospital or specialized clinic. Additionally, reliable venous access is crucial for the procedure, which can be challenging to maintain in some patients. The frequency and burden of LA significantly impact patients' quality of life, disrupting their daily routines, school, or work.

The therapeutic landscape for HoFH has evolved significantly with the introduction of novel lipid-lowering agents. Among these, Evinacumab has emerged as a very effective LLT. Evinacumab is a fully human monoclonal antibody that inhibits angiopoietin-like protein 3 (ANGPTL3), a key regulator of lipid metabolism [4-6]. ANGPTL3 inhibits lipoprotein lipase, an enzyme involved in the hydrolysis and clearance of triglyceride-rich lipoproteins [6, 7]. By inhibiting ANGPTL3, Evinacumab promotes lipoprotein clearance via LDL receptor-independent pathways; a relevant mechanism particularly in HoFH, where LDL receptor function is profoundly impaired or absent.

Clinical studies have demonstrated that Evinacumab can reduce LDL-C levels by approximately 50% in patients with HoFH, representing a substantial improvement compared to conventional LLTs [4-6]. These reductions can be expected to confer meaningful cardiovascular benefit. While the lipid-lowering efficacy of Evinacumab is well established, direct evidence of its impact on atherosclerotic disease progression remains to be established. Recent findings provide important mechanistic insights [8]. In this small retrospective imaging study, Evinacumab treatment in patients with HoFH appeared to be associated with reduced progression of coronary atherosclerotic



plaque, as assessed by serial coronary computed tomography angiography (CCTA).

In other patient populations with dyslipidemia, invasive intra-coronary imaging studies [9, 10] as well as non-invasive CCTA studies [11, 12] have substantiated that intensified LDL-C reduction by combining statin and PCSK9 inhibition translates into a greater regression of coronary atheroma volume coinciding with a more stable plaque phenotype. Extending this paradigm to HoFH is critical, particularly given the extreme lipid burden and the undefined optimal level of LDL-C reduction needed to effectively reduce the markedly elevated cardiovascular risk in this population. Although Schonck et al. [8] provided preliminary evidence suggesting that Evinacumab may attenuate progression of coronary atherosclerosis in HoFH patients attaining a time-weighted cumulative LDL-C levels lower than 3 mmol/L/year, validation in a larger prospective cohort, including control group, is warranted. Given the inherent challenges of conducting randomized placebo-controlled clinical trials powered for clinical outcomes in an ultra-rare disease, the use of validated surrogate endpoints such as CCTA is essential. CCTA offers a non-invasive, reproducible method to assess both total plaque burden and compositional features, thereby enabling robust evaluation of treatment effects. The EVOLVE-HoFH study was designed to build upon this initial evidence, aiming to further characterize the impact of Evinacumab on coronary plaque burden and phenotype in patients with HoFH using quantitative serial CCTA imaging.

Methods

Study Design and Rationale

EVOLVE-HoFH is a real-world, observational, multicenter, international, open-label study that combines retrospective and prospective data collection. The design is based on a comparison between an "intensified treatment group" (HoFH patients starting Evinacumab in clinical practice) and a "conventional treatment comparator group" (HoFH patients who, for reasons of access or personal choice, do not receive Evinacumab). This "real-world" approach leverages the natural variation in clinical practice across different countries, allowing for the collection of data on the drug's effectiveness in a generalizable context.

Study Population

Adolescent and adult patients (age ≥12 years) with a confirmed diagnosis (clinical or genetic) of HoFH (bi-allelic FH), according to the European Atherosclerosis Society (EAS) consensus panel criteria (1), will be enrolled. Patients must be on a stable baseline LLT for at least 30 days prior to the initiation of Evinacumab (intensified treatment group) or to a baseline CCTA (conventional treatment group), with an LDL-C level > 3.6 mmol/L (140 mg/dL), indicating a high residual cardiovascular risk despite maximal LLT. The target sample size is set at approximately 52 patients (35 in the intensified treatment group and 17 in the conventional treatment group); a number considered adequate to detect a clinically significant signal in an imaging study on an ultra-rare disease.

Study Periods and Data Collection

The study includes two key CCTA assessments**:** a baseline visit (visit 1) performed from 6 months prior to 1 month after the initiation of Evinacumab (for the treatment group) and a follow-up visit (visit 2) performed 18-24 months after the initiation of Evinacumab to assess changes over time. All clinical, laboratory, and imaging data will be collected via a centralized and secure electronic Case Report Form (eCRF).

Study Endpoints

Primary Endpoint: The difference in the change in percent of non-calcified plaque volume (%NCPV) between baseline and follow-up, as assessed by CCTA, in HoFH patients receiving intensified lipid lowering therapy including Evinacumab versus those managed with conventional lipid-lowering therapy under routine clinical care. This endpoint was chosen because non-calcified plaque, rich in lipids and inflammatory cells, is considered the main determinant of plaque instability and cardiovascular event risk. %NCPV is sensitive to treatment-related changes in atherosclerotic burden and able to capture early plaque modifications.

Secondary Endpoints: These include difference in the change in total plaque volume (TPV, an indicator of overall atherosclerotic burden), calcified plaque volume (CPV, an increase of which could indicate a "healing" and stabilization process), and percent atheroma volume (PAV) between baseline and follow-up within each treatment group and between the intensified treatment group and the conventional lipid-lowering treatment group. Additional endpoints include changes in high-risk plaque features (e.g., low attenuation plaque, positive remodeling), in segment involvement score and plaque phenotype (from non-calcified to calcified) and in LDL-C levels between baseline and follow-up, both within and between treatment groups. This will provide a comprehensive evaluation of plaque morphology and composition and metabolic response.

CCTA Analysis and Centralization

A methodological pillar of the study is the centralized analysis of all CCTA images. The use of validated Artificial Intelligence-based software to perform quantitative analysis of the CT-images (AI-QCT, Cleerly Inc.) provides an accurate and highly reproducible method allowing for absolute plaque quantification as well as evaluation of adverse plaque features (outward remodeling, low-attenuation plaque) [13, 14].

Statistical Analysis

The primary analysis will use linear regression models to compare the change in the primary endpoint between the two groups, adjusting for potential confounding factors such as age, sex, baseline LDL-C levels, and the use of concomitant therapies (e.g., Lomitapide, LA). This statistical approach aims to isolate the specific effect of Evinacumab. Safety analyses will be descriptive. A detailed Statistical Analysis Plan (SAP) will be finalized before the database lock.

Ethical Considerations

The study will adhere to the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Approval of the protocol by local Ethics Committees is a prerequisite for enrollment at each center. All participants must sign a written informed consent form after receiving a full and clear explanation of the objectives and procedures. Stringent measures will be implemented to protect patient data confidentiality and privacy.

Discussion

The EVOLVE-HoFH study employs a pragmatic approach; a strategic choice necessary to balance scientific rigor with the limitations of clinical research in ultra-rare diseases. In the context of HoFH, where randomized controlled trials (RCTs) on major clinical endpoints (MACE) are ethically and logistically unrealistic, innovative methodologies like this are a necessity to advance knowledge. This study aims to bridge the critical gap between the

established biochemical efficacy of Evinacumab (LDL-C reduction) and the demonstration of a direct anatomical impact on coronary atherosclerotic plaques, as validated surrogate of cardiovascular event risk.

The strength of the present study is the shift from a biochemical endpoint to a quantitative assessment of the atherosclerotic burden. The use of CCTA, enhanced by artificial intelligence-based analysis software, allows for an objective assessment of both total plaque burden as well as the presence of adverse plaque features predisposing to a higher coronary event risk. First, Non-calcified plaque volume (NCPV) has been shown to closely associate with future risk of major adverse cardiovascular events [14]. A reduction in NCPV following therapy has therefore been proposed as valuable surrogate to estimate clinical benefits of cardiovascular interventions; a concept which is currently being validated in large prospective randomized studies (Transform trial, NCT03296813). The ability to demonstrate stabilization or regression of NCPV after intensifying LLT with Evinacumab will be of great interest to treating physicians. This aligns with the concept of imaging-based treatment optimization [15], which provides strong mechanistic evidence of the drug's anti-atherosclerotic effects. Second, enhanced assessment of coronary atherosclerosis combining additional measures of plaque composition on top of plaque volume, has been shown to provide a further refinement in MACE prediction [15]. Third, an endpoint in an ultra-rare disease such as HoFH requires optimal reproducibility in order to allow detection of benefit in a modestly-sized intervention group. Traditionally, the use of serial CCTA has been hampered by relatively poor reproducibility [16], since visual assessment is invariably affected by reader experience and interobserver variability. The introduction of AI-QCT has markedly improved reproducibility of plaque-burden evaluation and stenosis detection [17, 18], thus allowing relevant findings despite the use of relatively small patient groups.

Alongside these strengths, the design has inherent limitations that must be acknowledged. The absence of randomization introduces a risk of confounding and selection bias. It is plausible that physicians may be more inclined to prescribe an innovative treatment such as Evinacumab to patients perceived to be at higher risk (confounding by indication). Although attempts will be made to mitigate this risk through careful construction of a comparator group and the use of statistical adjustment analyses, the possibility of unmeasured residual confounders (e.g., differences in lifestyle, adherence to other therapies, genetic background) cannot be ruled out. Furthermore, the "real-world" nature of the study, while increasing its external validity and generalizability to daily clinical practice, also introduces potential heterogeneity in baseline therapies and standards of care among the various centers, making it more complex to isolate the net effect attributable to Evinacumab alone.

In summary, the EVOLVE-HoFH study has the potential to provide crucial and highly relevant clinical information. In the event of a positive result, the demonstration of a regression or stabilization of coronary plaque would represent tangible and convincing evidence of the drug's effectiveness in modifying the atherosclerotic process. This would not only strengthen the rationale for the use of Evinacumab in this population but could also pave the way for the introduction of imaging-based treatment, allowing for the personalization and optimization of long-term management of these high-risk patients. By integrating advanced imaging and a pragmatic trial design, EVOLVE-HoFH not only addresses a critical clinical gap but also sets the stage for a new era of precision care in ultra-rare cardiovascular diseases.

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