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MINI REVIEW

# Evinacumab: Mechanism of action, clinical, and translational science

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**Abstract**

Homozygous familial hypercholesterolemia (HoFH) is a rare and serious genetic condition characterized by premature cardiovascular disease due to severely elevated low-density lipoprotein cholesterol (LDL-C). HoFH primarily results from loss-of-function (LOF) mutations in the LDL receptor (LDLR), reducing LDL-C clearance such that patients experience severe hypercholesterolemia, exacerbating the risk of developing cardiovascular events. Treatment options such as statins, lomitapide, ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, and apheresis help lower LDL-C; however, many patients with HoFH still fail to reach their target LDL-C levels and many of these lipid-lowering therapies are not indicated for pediatric use. Angiopoietin-like protein 3 (ANGPTL3) has been identified as a target to treat elevated LDL-C by acting as a natural inhibitor of lipoprotein lipase (LPL) and endothelial lipase (EL), enzymes involved in the hydrolysis of the triglyceride and phospholipid content of very low-density lipoproteins. Persons heterozygous for LOF mutations in ANGPTL3 were reported to have lower LDL-C than non-carriers and lower risk of coronary artery disease. Evinacumab is a first-in-class human monoclonal antibody that specifically binds to ANGPTL3 to prevent its inhibition of LPL and EL. In clinical trials, a 15 mg/kg intravenous dose every 4 weeks has shown a mean percent change from baseline in LDL-C of ~50% in adult, adolescent, and pediatric patients with HoFH. This mini review article describes the mechanism of action of evinacumab, evinacumab population PK and PD modeling, and clinical development history of evinacumab for the treatment of HoFH.

## INTRODUCTION

Homozygous familial hypercholesterolemia (HoFH) is a rare and serious genetic condition with autosomal dominant inheritance that is characterized by premature cardiovascular (CV) disease due to severely elevated low-density lipoprotein cholesterol (LDL-C).[1,2] HoFH primarily results from loss-of-function (LOF) mutations in the low-density lipoprotein (*LDLR*) gene,[3] which can be categorized as either true homozygotes, compound

heterozygotes, or double heterozygotes based on the affected alleles. These mutations result in defective LDLR, causing impaired clearance of LDL from circulation by hepatocytes. Accumulation of LDL leads to severe hypercholesterolemia and results in the build-up of atherosclerotic plaques, increasing the risk of CV events.

Observational studies in HoFH have shown the mean age of initial CV events was around 20 years of age, and its impact in younger patients, underscoring the need for early aggressive and effective intervention in HoFH, especially in pediatrics.[1,3–5] Illustrating the clinical severity of HoFH, six patients on the CASCADE FH registry, a contemporary cohort of people with HoFH from across the United States, have undergone liver transplantation between the ages of 4 and 18 years. At the time of liver transplant, these patients were 4, 6, 8, 15, 17, and 18 years of age.[2] Standard-of-care treatment options for HoFH include statins, lomitapide, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and lipoprotein apheresis. However, statins, ezetimibe, and PCSK9 inhibitors are LDLR-dependent, and thus patients with HoFH that have null-null *LDLR* variants respond poorly, if at all, to these therapies.[6–12] Additionally, some lipid-lowering therapies (LLTs; e.g., lomitapide) are not indicated for pediatric use. Consequently, many patients with HoFH still fail to reach their target LDL-C levels.

Angiopoietin-like protein 3 (ANGPTL3) is a secreted protein that is almost exclusively expressed in the liver.[13] ANGPTL3 has been shown to reduce the activity of lipoprotein lipase (LPL) and endothelial lipase (EL) in vitro and in vivo, enzymes that are involved in the hydrolysis of the triglyceride (TG) and phospholipid content of very low-density lipoproteins (VLDL), respectively.[14–20] Genetic studies have shown that carriers of LOF variants in ANGPTL3 present with low levels of plasma LDL-C, high-density lipoprotein cholesterol, and TGs.[21] Persons heterozygous for LOF mutations in ANGPTL3 were reported to have lower levels of ANGPTL3 and LDL-C than non-carriers, conferring a 39% lower risk of coronary artery disease.[22] Therefore, inhibiting ANGPTL3 was hypothesized to result in clinically meaningful LDL-C reductions and subsequently improve CV outcomes. Evinacumab is a first-in-class human monoclonal antibody that specifically binds to ANGPTL3 and blocks its inhibition of LPL and EL (Figure 1).[19] In clinical trials, a 15 mg/kg intravenous (i.v.) dose of evinacumab administered every 4 weeks led to an ~50% mean LDL-C reduction from baseline in adult, adolescent, and pediatric patients with HoFH.[23] The pharmacokinetics (PK) of evinacumab has consistently shown a profile consisting of both linear and non-linear target-mediated elimination. This review article describes the mechanism of action of evinacumab by which ANGPTL3

**Clinical and Translational Card for Evinacumab**

- **Mechanism of action**: Evinacumab is a recombinant human monoclonal antibody that binds to and inhibits angiopoietin-like protein 3 (ANGPTL3). ANGPTL3 is a member of the angiopoietin-like protein family that is expressed primarily in the liver and plays a role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). Evinacumab inhibition of ANGPTL3 leads to reduction in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Evinacumab reduces LDL-C independent of the presence of LDL receptor by promoting very low-density lipoprotein processing and clearance upstream of LDL formation. Evinacumab blockade of ANGPTL3 lowers TG and HDL-C by rescuing LPL and EL activities, respectively.
- **Indication(s)**: Indicated as an adjunct to other LDL-C lowering therapies for the treatment of adult and pediatric patients, aged 5 years and older, with homozygous familial hypercholesterolemia.
- **Dosage and administration**: 15 mg/kg administered by intravenous (i.v.) infusion once monthly (every 4 weeks).
- **Major metabolic pathway (if feasible)**: As a human monoclonal immunoglobulin (Ig)G4 antibody, evinacumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. Given that the metabolic pathways for protein-based therapeutics are generally well understood, specific metabolism studies have not been performed for evinacumab, which is in accordance with International Conference on Harmonisation S6 (R1) guidelines.
- **Key pharmacokinetic characteristics**: The pharmacokinetics of evinacumab is characterized by both linear and non-linear saturable elimination. At the approved dose regimen of 15 mg/kg i.v. administered every 4 weeks, the population pharmacokinetic predicted mean steady-state area under the concentration–time curve for a dosing interval is 10,286 day*mg/L. The predicted steady-state maximum concentration and trough concentration are 689 and 240.7 mg/L, respectively.

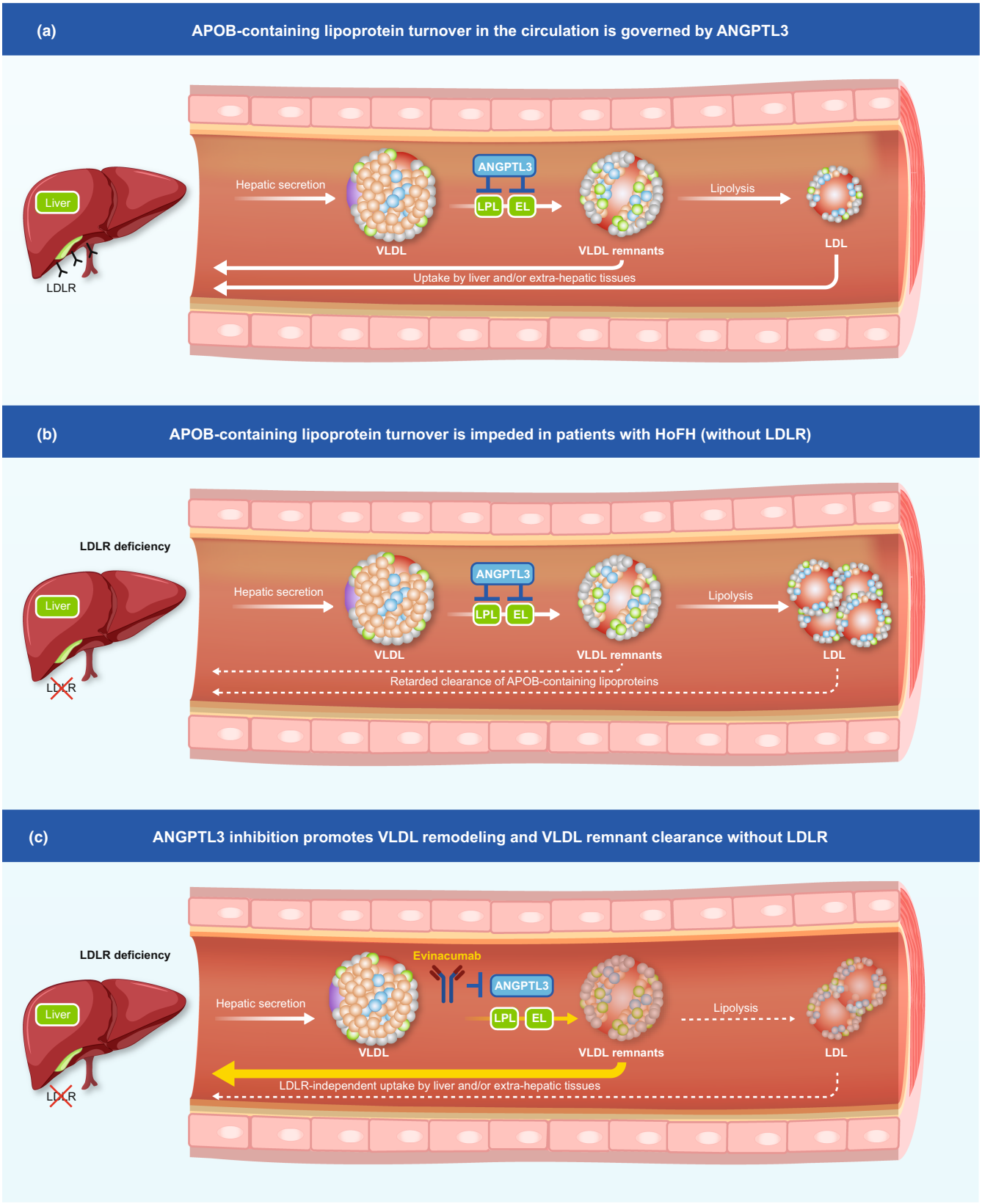


**FIGURE 1** Mechanism of action of ANGPTL3 and evinacumab in lipoprotein metabolism. (a) Effect of ANGPTL3 on APOB-containing lipoprotein turnover. (b) APOB-containing lipoprotein metabolism in patients with HoFH. (c) Effect of ANGPTL3 inhibition on lipoprotein metabolism in the absence of LDLR. ANGPTL3, angiopoietin-like protein 3; APOB, apolipoprotein B; EL, endothelial lipase; HoFH, homozygous familial hypercholesterolemia; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein cholesterol.

inhibition reduces LDL-C, evinacumab PK, and pharmacodynamics (PD) and clinical development history of evinacumab for the treatment of HoFH.

## REGULATORY APPROVAL HISTORY

Evinacumab is currently approved in multiple countries as an adjunct to other LDL-C lowering therapies for the treatment of patients with HoFH ≥5 years of age at an approved dose of 15 mg/kg i.v. administered every 4 weeks.

Evinacumab was first approved in the United States (as evinacumab-dgnb) by the Food and Drug Administration (FDA) on February 11, 2021, with a recommended dose of 15 mg/kg i.v. administered every 4 weeks as an adjunct to other LDL-C lowering therapies for the treatment of patients with HoFH aged 12 years and older. The initial approval of evinacumab was extended to patients with HoFH aged 5–11 years by the FDA on March 21, 2023.

On June 17, 2021, evinacumab was approved for use in the European Union/European Economic Area by the European Medicines Agency (EMA) as an adjunct to diet and other LDL-C lowering therapies for the treatment of patients with HoFH aged 12 years and older, with a recommended dose of 15 mg/kg i.v. administered every 4 weeks; the EMA approval of evinacumab was extended to patients with HoFH aged 5–11 years on December 11, 2023. Within the UK, the Medicines and Healthcare Products Regulatory Agency approved evinacumab on August 26, 2022, as an adjunct to diet and other LDL-C lowering therapies for the treatment of adults and adolescent patients aged 12 years and older with HoFH, with a recommended dose of 15 mg/kg i.v. administered every 4 weeks.

A new drug submission for evinacumab was approved by Health Canada on September 22, 2023, as an adjunct to diet and other LDL-C lowering therapies for the treatment of adult and pediatric patients ≥5 years of age with HoFH, also with a recommended dose of 15 mg/kg i.v. administered every 4 weeks.

In Japan, evinacumab was granted orphan drug designation for familial hypercholesterolemia (homozygous) as the planned indication. A Japan new drugs application with priority review was submitted to the Pharmaceuticals and Medical Devices Agency for the treatment of HoFH in patients >5 years of age; approval was received on January 18, 2024, to treat patients of all ages.

Marketing authorization applications for evinacumab are currently under review by the Brazilian Health Regulatory Agency, the Comisión Federal para la Protección contra Riesgos Sanitarios in Mexico, and the Ministry of Health in Israel. In 2024, marketing authorization applications are planned for Argentina, Columbia, Kingdom of Saudi Arabia, and Kuwait.

## MECHANISM OF ACTION

The mechanism of action of evinacumab in the treatment of HoFH is driven by the inhibition of ANGPTL3, resulting in the reduction of LDL-C in circulation independent of LDLR. ANGPTL3 is an inhibitor of two vascular lipases – LPL and EL, that hydrolyze circulating TGs and phospholipids, respectively.[14,17] The EL was originally discovered as an enzyme that regulates high-density lipoprotein metabolism;[24] however, recently EL was shown to be involved in catabolism of apoliopoprotein B-containing lipoproteins, VLDL and LDL.[18,25] In healthy adults, VLDL are secreted by hepatocytes into circulation and undergo lipolysis by LPL and EL, leading to the formation of VLDL remnants that can be taken up by the liver through LDLR and remnant receptors, or further hydrolyzed into LDL which, in turn, is cleared through LDLR.[26] HoFH results in defective LDLR, causing impaired clearance of LDL by hepatocytes and increased levels of LDL-C in the circulation.

Evinacumab binds to and inhibits the ANGPTL3, thereby blocking ANGPTL3 inhibition of LPL and EL.[19] EL activation with evinacumab appears to be critical for its effect on VLDL remodeling and clearance in HoFH.[18] Downstream, blockade of ANGPTL3 with evinacumab results in a reduction in LDL-C, as observed in multiple clinical trials.[27] More specifically, ANGPTL3 inhibition promotes VLDL processing, resulting in the formation of lipid-depleted VLDL remnant particles, which accelerates their clearance from the circulation. This, in turn, leads to depletion of the LDL precursor pool and reduces LDL-C level independent of LDLR.[18] In addition to the reduction in LDL, evinacumab administration leads to increased hydrolysis of TG and lowering of TG levels, which can be used as a direct PD measurement related to the inhibition of ANGPTL3. The mechanism of action of ANGPTL3 and the effect of evinacumab inhibition of ANGPTL3 in HoFH is illustrated in Figure 1.

## PHARMACOKINETIC/ PHARMACODYNAMIC CHARACTERISTICS

The PK and PD of evinacumab have been studied across clinical studies in pediatric, adolescent, and adult patients with HoFH, and healthy adult participants. The concentration–time profile of evinacumab is typical of an antibody characterized by both linear and non-linear target-mediated elimination in both healthy participants and participants with HoFH (Figure 2). The PD of evinacumab was assessed via LDL-C as the primary efficacy end point, and via measurement of total ANGPTL3 as a reflection of target engagement.

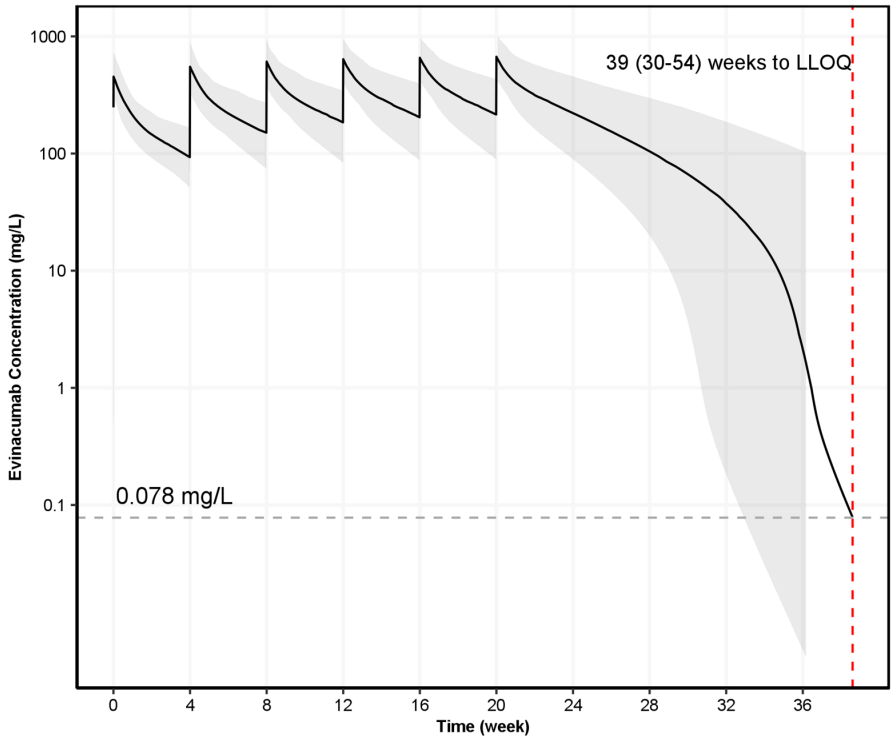


**FIGURE 2** Simulated evinacumab concentration–time profile following repeat doses of 15 mg/kg i.v. every 4 weeks. *Note*: Red dashed line is 39 weeks after the first dose when median concentration falls below LLOQ, 30–54 weeks is the predicted range; gray dashed line is 0.078 mg/L of the LLOQ level. Gray shaded region is the 2.5–97.5%, which was cut at around 36 weeks due to the lower-bound (2.5%) exceeding the plotting limit. i.v., intravenously; LLOQ, lower limit of quantitation.

After administration of evinacumab 15 mg/kg i.v. every 4 weeks, steady-state trough concentrations are reached after four doses, with an accumulation ratio of approximately two. Population PK modeling has estimated the mean (standard deviation) steady-state concentration to be 266 (120) mg/L in adults, with a mean (standard deviation) maximum concentration of 718 (183) mg/L. in pediatric patients, the mean (standard deviation) steady-state concentration is estimated to be 174 (74.1) mg/L, with a mean (standard deviation) maximum concentration of 444 (111) mg/L. The presence of non-linear clearance results in a 4.3-fold increase in area under the concentration–time curve at steady state when the dose is increased threefold. The steady-state volume of distribution was estimated to be 4.7 L in adult patients.[28]

Mean concentrations of total evinacumab have been shown to be comparable over time across Japanese and Caucasian ethnicities, with no notable differences in exposure following i.v. and subcutaneous doses. Similarly, the safety and the effect of evinacumab on LDL-C were comparable across ethnicities.[29] Across age groups, concentrations of evinacumab gradually decreased with decreasing age, consistent with the effect of lower body weight with weight-based dosing.[28,30] However, exposure in pediatric patients was within the range of exposure in adult patients and LDL-C reduction was very consistent across age groups.

Population PK and PK/PD analyses of the clinical PK/PD data were conducted to characterize the PK/PD of evinacumab in adults.[31] The PK of evinacumab was characterized by a two-compartment model with parallel linear and non-linear elimination pathways. Steady state was achieved after multiple doses of evinacumab, and evinacumab is cleared via linear, and saturable, non-linear mechanisms. The final population PK model included allometrically scaled clearance and volume of distribution terms, with a fixed exponent of 0.75 on clearance, and an exponent of 0.857 on volume. Covariates found to be significant in the PK model included the effect of disease state and baseline ANGPTL3 concentrations on the maximum target-mediated rate of elimination. The magnitude of covariate effects on derived evinacumab exposure for patients with extreme baseline ANGPTL3 or body weight values is not expected to deviate significantly from a typical patient with HoFH nor to be clinically meaningful. Evinacumab PK/PD was characterized by an indirect exposure–response model with saturable inhibition of LDL-C production driven by evinacumab. Covariates incorporated in the final PK/PD model included the effect of a higher baseline LDL-C, which was associated with a smaller half-maximal inhibitory concentration, and lower baseline body weight and Caucasian race, which were both associated with an increase in the maximum drug-induced inhibitory effect.

To support the selection of the 15 mg/kg i.v. every 4 weeks dosing regimen, simulations were performed using the population PK/PD model developed using clinical PK/PD data to assess the median percentage of patients receiving evinacumab 15 mg/kg i.v. every 4 weeks who attain a target LDL-C concentration <100 mg/dL and the median percentage of patients who achieve a >30%, 50%,

**TABLE 1** Simulated percentage of patients with HoFH achieving various goals of LDL-C reduction at Week 24 following evinacumab administration every 4 weeks.

| | LDL-C % reduction from baseline | | | | | | LDL-C < 100 mg/dL | |
|---|---|---|---|---|---|---|---|---|
| | 30% | | 50% | | 70% | | | |
| i.v. every 4 weeks | Median (%) | Range (%) | Median (%) | Range (%) | Median (%) | Range (%) | Median (%) | Range (%) |
| 5 mg/kg | 53.7 | 36.8–68.4 | 29.5 | 14.7–42.1 | 4.2 | 0.00–11.6 | 20.0 | 8.4–33.7 |
| 15 mg/kg | 84.2 | 70.5–94.7 | 63.2 | 46.3–76.8 | 14.7 | 6.3–27.4 | 36.8 | 23.2–51.6 |
| 20 mg/kg | 88.4 | 74.7–96.8 | 69.5 | 52.6–81.1 | 17.9 | 6.3–28.4 | 40.0 | 25.3–55.8 |

*Note*: Simulations were performed for 1000 trials with 95 patients/trial, using distribution of observed covariates.[31]

Abbreviations: HoFH, homozygous familial hypercholesterolemia; i.v., intravenous; LDL-C, low-density lipoprotein cholesterol.

**TABLE 2** Summary of key clinical trials in patients with homozygous familial hypercholesterolemia.

| Study phase/population | Study design | Posology (number of patients) |
|---|---|---|
| Phase II | | |
| Patients with HoFH who are not currently undergoing LDL apheresis therapy (NCT02265952) | Open-label, single-arm, proof-of-concept study to evaluate the safety and efficacy and multiple doses of evinacumab in patients with HoFH | Main study period:<br>• Day 1: 250 mg s.c. × 1 dose<br>• Day 15: 15 mg/kg i.v. × 1 dose<br>• Day 85: 450 mg s.c. QW × 4 doses<br>• Open-label extension (from start of main study)<br>• Week 26: 300 mg s.c. QW × 4 doses<br>• Week 38: 20 mg/kg i.v. × 1 dose<br>• Week 58: 20 mg/kg i.v. Q12W<br>• Evinacumab $n = 9$ |
| Phase III | | |
| Patients with HoFH (NCT03399786) | Randomized, 24-week, double-blind, placebo-controlled study with a 24-week open-label extension period | • 15 mg/kg i.v. Q4W<br>• Placebo i.v. Q4W<br>• Evinacumab $n = 43$, Placebo $n = 22$ |
| Patients with HoFH (NCT03409744) | Open-label safety and efficacy study including patients from previous studies and evinacumab naïve patients | • 15 mg/kg i.v. Q4W<br>• Evinacumab $N = 116$ |
| Pediatric | | |
| Patients 5 to <12 years of age with HoFH (NCT04233918) | Three part, open-label efficacy, safety, and pharmacokinetic study of evinacumab in pediatric patients | • 15 mg/kg i.v. Part A (evinacumab $n = 6$)<br>• 15 mg/kg i.v. Q4W Part B (evinacumab $n = 14$)<br>• 15 mg/kg i.v. Q4W Part C (evinacumab $n = 20$) |

Abbreviations: HoFH, homozygous familial hypercholesterolemia; i.v., intravenous; LDL, low-density lipoprotein; QW, every week; Q4W, every 4 weeks; Q12W, every 12 weeks; s.c. subcutaneous.

or 70% reduction in LDL-C from baseline (Table 1). After evinacumab 15 mg/kg i.v. infusions every 4 weeks, 36.8% of simulated patients attained LDL-C concentrations <100 mg/dL. Additionally, 63.2% of simulated patients were predicted to attain a percent reduction on LDL-C of ≥50%, providing substantial clinical benefit in reducing LDL-C and attaining the target reductions recommended in clinical practice guidelines. Simulations were also performed for a 5 mg/kg and a 20 mg/kg i.v. every 4 weeks dose regimen. Generally, a 5 mg/kg dose regimen showed notably inferior efficacy, while a 20 mg/kg dose regimen did not show a major benefit over 15 mg/kg, confirming the optimal dose of 15 mg/kg.

## KEY CLINICAL TRIALS

An overview of key clinical trials in the development of evinacumab for the treatment of HoFH is presented in Table 2. Proof-of-concept was established in an open-label phase II study in patients with HoFH (NCT02265952). The benefit risk of evinacumab in the treatment of HoFH was established in two pivotal phase III trials in adult and adolescent patients ≥12 years of age, and a phase I/III trial in pediatric patients 5 to <12 years of age. NCT03399786 was a pivotal double-blind, placebo-controlled study in adult and adolescent patients (12 to <18 years) with HoFH, containing a 24-week double-blind treatment period and

a 24-week open-label treatment period. Patients were administered evinacumab 15 mg/kg i.v. or placebo every 4 weeks. NCT03409744 was a long-term, open-label safety and efficacy study in adults and adolescent patients receiving 15 mg/kg i.v. every 4 weeks. NCT04233918 was a three-part study assessing the PK, safety, and efficacy of evinacumab in pediatric patients 5 to <12 years of age. Part A assessed the PK and safety of a single 15 mg/kg i.v. dose of evinacumab. Part B assessed the safety, PK, and efficacy of the 15 mg/kg i.v. every 4 weeks dose regimen, and Part C was an open-label extension to assess long-term safety and efficacy in patients from both Part A and Part B. A dose regimen of 15 mg/kg i.v. every 4 weeks was selected based on the totality of safety, efficacy, and PK data from phase I and phase II, supported by the population PK/PD modeling and simulation.

Key inclusion criteria were consistent across phase III studies and included a documented functional mutation in both *LDLR* alleles or documented homozygous or compound heterozygous mutations in apolipoprotein B or PCSK9. Additionally, participants were required to have untreated total cholesterol >500 mg/dL and TGs <300 mg/dL and both parents were required to have documented total cholesterol >250 mg/dL. Key exclusion criteria were selected to prevent confounding of efficacy results and included unstable use of background LLTs, including apheresis, for a sufficient period prior to screening. This generally included stable use of PCSK9 inhibitors for 8 weeks, fibrates for 6 weeks, mipomersen for 24 weeks, and a stable apheresis schedule for 8 weeks. Additionally, patients were excluded for the presence of clinically significant uncontrolled endocrine diseases known to influence serum lipids or lipoproteins.

## SUMMARY OF CLINICAL EFFICACY AND SAFETY

The safety and efficacy of evinacumab has been assessed across multiple clinical trials in healthy participants, participants with elevated TGs, and patients with HoFH. The primary efficacy end point to support clinical benefit is the percent change in LDL-C from baseline at Week 24 in patients with HoFH. LDL-C was chosen as the primary efficacy end point based on the body of evidence implicating LDL-C in the development of downstream CV disease, including genetic studies, observational studies, and mechanistic studies in nonclinical models.[19,22]

In NCT03399786, treatment with evinacumab 15 mg/kg i.v. every 4 weeks in adult and adolescent patients (aged 12 to <18 years) resulted in a statistically significant decrease in percent change from baseline of LDL-C, with a mean reduction from baseline of −47.1% (least-squares mean difference versus placebo of −49.0%; $p < 0.0001$).[23] Reduction in LDL-C was first observed by Week 2, and consistent efficacy was observed through Week 24. This effect was replicated in the long-term safety and efficacy trial (NCT03409744), where the percent reduction from baseline was −43.7%.[32] The effect of evinacumab on LDL-C reduction was also comparable in pediatric patients where treatment with evinacumab resulted in a −48.3% reduction (NCT04233918).[33]

Pooling safety data across placebo-controlled trials of evinacumab in patients with HoFH, the percentage of patients who experienced any treatment-emergent adverse event was relatively balanced across groups. The most common treatment-emergent adverse event occurring in a greater percentage of patients receiving evinacumab compared with placebo were nausea, pain in the extremity, influenza-like illness, and dizziness.[23,33–35] The incidence of anti-evinacumab antibody formation has been low across all age groups. One pediatric patient who was 5 to <12 years of age developed treatment-emergent antidrug antibody; however, the PK and clinical efficacy of evinacumab were not affected.[33]

The cumulative safety and efficacy results from the phase III studies confirmed the selection of 15 mg/kg i.v. every 4 weeks as an appropriate dose regimen. A similar dose response for evinacumab was observed with other lipid moieties such as TG. Maximal TG reduction occurred rapidly following administration of evinacumab, and increasing evinacumab concentrations resulted in dose-dependent decreases in TG.[36] Similar to the dose response observed with LDL-C, no further meaningful reduction in TG was observed at doses higher than 15 mg/kg i.v., confirming the dose regimen.

## FUTURE PROSPECTS

Approval of evinacumab is being pursued in countries across the world to bring this important drug to patients. Further population PK and PK/PD modeling may be carried out to characterize the effect of evinacumab on LDL-C in pediatric and adolescent patients.

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### CONFLICT OF INTEREST STATEMENT

All authors are employees of and stockholders in Regeneron Pharmaceuticals, Inc.

## DATA AVAILABILITY STATEMENT

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc.), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

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