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ADISINSIGHT REPORT

Evinacumab: First Approval

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Abstract
The recombinant human monoclonal antibody evinacumab (evinacumab-dgnb, EVKEEZA™) is an angiopoietin-like protein three (ANGPTL3) inhibitor that has been developed by Regeneron Pharmaceuticals for the treatment of homozygous familial hypercholesterolaemia (HoFH), refractory hypercholesterolemia (both familial and non-familial) and severe hypertriglyceridaemia. Based on the results of the phase III ELIPSE HoFH trial, evinacumab was recently approved in the USA as an adjunct to other LDL-C lowering therapies for the treatment of adult and paediatric patients aged 12 years and older with HoFH, and has received a positive opinion in the EU. This article summarizes the milestones in the development of evinacumab leading to this first approval for HoFH.

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Evinacumab (EVKEEZA™): Key points

An angiopoietin-like three (ANGPTL3) inhibitor that has been developed by Regeneron Pharmaceuticals for the treatment of homozygous familial hypercholesterolaemia (HoFH).

Received its first approval on 11 February 2021 in the USA.

Approved for use as an adjunct to other LDL-C lowering therapies for the treatment of adult and paediatric patients aged 12 years and older with HoFH.

1 Introduction

Evinacumab (evinacumab-dgnb, EVKEEZA™) is a recombinant human monoclonal antibody that inhibits angiopoietin-like protein three (ANGPTL3) that has been developed by Regeneron Pharmaceuticals for the treatment of homozygous familial hypercholesterolaemia (HoFH), refractory hypercholesterolemia (both familial and non-familial) and severe hypertriglyceridaemia. ANGPTL3 prevents lipid metabolism via inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL) leading to increased plasma triglyceride (TG) low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C) levels [1, 2]. Inhibition of ANGPTL3 preserves the activity of LPL and EL, leading to reduced TG, LDL-C and HDL-C levels in plasma, independently of the LDL receptor [3, 4].

An IV injection formulation of evinacumab received is first approval on 11 February 2021 in the USA for use as an adjunct to other LDL-C lowering therapies for the treatment of adult and paediatric patients aged 12 years and older with HoFH [1, 5] and has received a positive opinion in the EU [6]. The recommended dose of evinacumab in the USA is 15 mg/kg IV once every 4 weeks [5].

1.1 Company Agreements

In November 2007 Regeneron entered into a global strategic collaboration agreement with Sanofi-Aventis to discover, develop and commercialize fully-human therapeutic antibodies utilizing Regeneron's proprietary VelociSuite of technologies (including VelocImmune®) with Sanofi-Aventis having the exclusive option to co-develop each drug candidate discovered as part of the collaboration [7]. This agreement was expanded and extended in 2009 [8]. Sanofi did not opt-in or elected not to continue to co-develop evinacumab but remains entitled to receive a mid-single digit royalty on any future sales.

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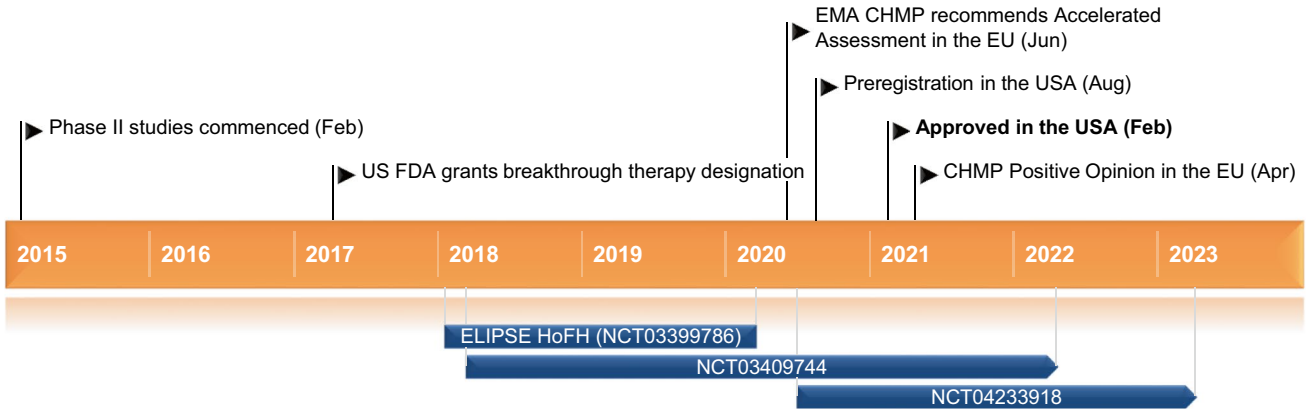

Key milestones in the development of evinacumab for the treatment of homozygous familial hypercholesterolaemia. *CHMP* Committee for Medicinal Products for Human Use, *EMA* European Medicines Agency, *FDA* Food and Drug Administration

2 Scientific Summary

2.1 Pharmacodynamics

Using surface plasmon resonance in vivo evinacumab bound to human, murine, rat and monkey ANGPTL3 with K_D values between 0.26 and 1.28 nmol/L. IC_{50} values for evinacumab blockade of human, murine, rat and monkey ANGPTL3-induced inhibition of LPL activity in vitro were between 1.0 and 13.6 nmol/L [9].

In vivo administration of a single 10 mg/kg IV dose of evinacumab increased post-heparin LPL activity 1.8 and 2.5-fold in normolipidaemic C57Bl/6 mice and in dyslipidaemic *db*/*db* mice, respectively, with no change in hepatic lipase activity. In *db*/*db* mice evinacumab significantly decreased plasma TG and total cholesterol levels ($p < 0.0001$ and $p < 0.01$, respectively). In dyslipidaemic C57Bl/6 mice fed a high fat, high cholesterol diet, 8 weeks' treatment with evinacumab 25 mg/kg/week was associated with a marked and sustained reduction in circulating TG levels as well as significant reductions in total cholesterol and LDL-C levels, but did not affect TG levels in liver, adipose, or heart. In mice that do not express EL ($Lipg^{-/-}$) evinacumab significantly reduced plasma TG levels but did not affect serum HDL-C, indicating that EL mediates the HDL-C lowering effects of the antibody. In dyslipidaemic cynomolgus monkeys administration of a single dose of evinacumab 3 or 10 mg/kg was associated with rapid and marked dose-dependent decreases in plasma TG, non-HDL-C, and HDL-C levels [9].

Features and properties of evinacumab	
Alternative names	EVKEEZA™, evinacumab-dgnb, REGN-1500
Class	Antihyperlipidaemics, monoclonal antibodies
Mechanism of Action	ANGPTL3 inhibitor
Route of Administration	IV
Pharmacodynamics	Binds to and inhibits ANGPTL3 (K_D 0.26–1.28 nmol/L; IC_{50} 1.0–13.6 nmol/L); decreases plasma triglyceride, total cholesterol and LDL-C levels
Pharmacokinetics	AUC_τ 5923.7 d·µg/mL, C_{max} 553.9 µg/mL, t_{max} 0.1 day
Adverse events	
Most frequent	Nasopharyngitis, infusion reactions, influenza like illness, dizziness, rhinorrhoea, nausea, pain in extremity, asthenia, constipation, upper respiratory tract infection, nasal congestion, abdominal pain
Rare	Anaphylaxis
ATC codes	
WHO ATC code	A16A
EphMRA ATC code	A16A
Chemical Name	Immunoglobulin G4-kappa, anti-(human angiopoietin-related protein 3 (angiopoietin 5, ANG-5, angiopoietin-like protein 3)); human monoclonal antibody: γ4 heavy chain (1–453) [human VH (IGHV3-43*02 (93%)–(IGHD)-IGHJ3*02) [8.8.19] (1–126)–IGHG4*01 H S108>P (234) (127–453)] (140–214')-disulfide with kappa light chain (1'–214') [human V-KAPPA (IGKV1-5*03 (99%)–IGKJ2*01) [6.3.9] (1'–107') -IGKC*01 (108'-214')] dimer (232–232'':235–235'')-bisdisulfide

2.2 Pharmacokinetics

In a phase I trial (NCT03146416) evinacumab administered at the recommended dose to Caucasian patients (n = 9) had mean AUC_{τ} and C_{max} of 5923.7 d·µg/mL and 553.9 µg/mL, respectively, and a t_{max} of 0.1 day after the first of two doses. Similar values were observed in a cohort of Japanese patients (n = 9) [10].

In a further study, steady state was reached after four doses of evinacumab at the recommended dose with an accumulation ratio of 2. Population pharmacokinetic modelling indicated a mean steady-state trough concentration of 241 µg/mL and a mean C_{max} at the end of infusion of 689 µg/mL. The estimated total volume of distribution is ≈ 4.8 L. The median time for serum evinacumab concentrations to decrease below the lower limit of quantitation (78 ng/mL) was 19 weeks after the last dose [5].

In a single 15-year-old patient with HoFH treated with evinacumab at the recommended dose, steady-state trough and end-of-infusion concentrations were in the same range observed in adult patients [5].

A population pharmacokinetic analysis based on data from volunteers (n = 183) and patients with HoFH (n = 95) indicates that age, gender, body weight and ethnicity have no clinically significant effect on the exposure of evinacumab [5].

2.3 Therapeutic Trials

2.3.1 Hypercholesterolemia

2.3.1.1 Phase III Treatment with evinacumab significantly reduced LDL-C levels compared to placebo in patients with HoFH in the double-blind phase III ELIPSE HoFH (NCT03399786). Patients who were receiving stable lipid-lowering therapy at the maximum tolerated dose were randomized to 24 weeks' treatment with evinacumab at the recommended dose (n = 43) or placebo (n = 22) [4]. A 47.1% reduction in LDL-C levels between baseline and week 24 was observed in patients treated with evinacumab compared to a 1.9% increase in placebo recipients ($p < 0.001$). Reduced LDL-C levels were evident from the first post-treatment lipid assessment (week 2) in patients treated with evinacumab. Evinacumab lowered cholesterol levels to a greater extent than placebo in patients with both null-null LDL-receptor variants (15 evinacumab and 6 placebo recipients) and non-null variants [4].

Key clinical trials of evinacumab (Regeneron Pharmaceuticals)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Evinacumab, placebo	Homozygous familial hypercholesterolaemia	Phase III	Completed	Multinational	NCT03399786, EudraCT2017-001388-19, ELIPSE HoFH
Evinacumab	Homozygous familial hypercholesterolaemia in paediatric patients	Phase III	Ongoing	Multinational	NCT04233918, EudraCT2019-001931-30
Evinacumab	Homozygous familial hypercholesterolaemia	Phase III	Ongoing	Multinational	NCT03409744, EudraCT2017-003170-13
Evinacumab, placebo	Hypercholesterolaemia	Phase II	Completed	Multinational	NCT03175367, EudraCT2017-001508-31
Evinacumab	Homozygous familial hypercholesterolaemia (lipoprotein kinetics)	Phase II	Completed	Netherlands, USA	NCT04722068
Evinacumab, placebo	Severe hypertriglyceridaemia with risk of pancreatitis	Phase II	Completed	Multinational	NCT03452228, EudraCT2016-003307-62
Evinacumab	Homozygous familial hypercholesterolaemia	Phase II	Completed	Canada, USA, Netherlands	NCT02265952, EudraCT2016-000411-32
Evinacumab, placebo	Hypertriglyceridaemia, Hypercholesterolaemia	Phase I	Completed	USA	NCT02107872
Evinacumab, placebo	Hypertriglyceridaemia, Hypercholesterolaemia	Phase I	Completed	USA	NCT01749878
Evinacumab, placebo	Safety and tolerability in volunteers	Phase I	Completed	USA	NCT03146416

Sixty-four patients who completed the double-blind treatment period in this study entered a subsequent 24-week open label treatment phase receiving IV evinacumab at the recommended dose. At 48 weeks LDL-C levels were 42.7% and 55.8% lower than baseline in patients who had received evinacumab (n = 44) and placebo (n = 20), respectively in the double-blind phase. The reduction in LDL-C levels was similar in patients with nul-nul and non-null receptor variants [11].

2.3.1.2 Phase II Treatment with evinacumab significantly reduced LDL cholesterol levels compared to placebo in patients with hypercholesterolaemia (mostly HoFH) refractory to maximum tolerated doses of statins and other lipid-lowering therapies in a double-blind phase II trial (NCT03175367). Patients were randomized to treatment with SC evinacumab 450 (n = 40) or 300 mg (n = 42) weekly, or 300 mg once every 2 weeks (n = 39) or SC placebo (n = 39); or IV evinacumab 15 (n = 38) or 5 mg/kg (n = 35) once every four weeks or IV placebo (n = 33). After 16 weeks LDL-C levels was reduced by 47.2%, 44.0% and 38.5% from baseline in patients treated with SC evinacumab 450 weekly and 300 mg once or twice weekly, respectively compared to an 8.8% increase in the placebo group ($p < 0.001$ vs. the two evinacumab once weekly regimens). In patients treated with IV evinacumab 15 and 5 mg/kg LDL-C levels were reduced by 49.9% and 23.5%, respectively compared to a 0.6% increase with placebo ($p < 0.001$ vs the higher evinacumab dose) [12].

2.4 Adverse Events

Adverse reactions occurring in > 3% of patients treated with evinacumab (n = 81) and with a greater incidence than in placebo recipients (n = 54) in two 24-week trials included nasopharyngitis (16% and 13% of evinacumab and placebo recipients, respectively), influenza like illness (7% and 6%), dizziness (6% and 0%), rhinorrhoea (5% and 0%), nausea (5% and 2%), pain in extremity (4% and 0%) and asthenia (4% and 0%). Other adverse reactions occurring in < 3% of evinacumab recipients and at a greater incidence than in placebo recipients included constipation, upper respiratory tract infection, nasal congestion, and abdominal pain. Two percent of patients treated with evinacumab required discontinuation of treatment because of adverse reactions including one case of anaphylaxis [5].

Infusion reactions including infusion site pruritus, pyrexia, muscular weakness, nausea, and nasal congestion occurred in 7% of evinacumab recipients and 4% of placebo recipients [5].

Antibody assays did not detect treatment emergent antibodies to evinacumab in any patients participating in these trials [5].

2.5 Ongoing Clinical Trials

Phase III studies are underway evaluating the long-term safety and efficacy of evinacumab in patients > 12 years of age with HoFH (NCT03409744) and efficacy and safety in paediatric patients (aged 5–11 years) with HoFH (NCT04233918).

3 Current Status

Evinacumab received its first approval on 11 February 2021 as an adjunct to other LDL-C lowering therapies for the treatment of adult and paediatric patients aged 12 years and older with HoFH in the USA [1].

Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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