FH Europe Foundation

7th August 2024

Response Statement on behalf of FH Europe Foundation

regarding the recent decision on ANGPTL3 inhibitor (Evinacumab) for patients with homozygous familial hypercholesterolaemia (HoFH) aged 12 years and older in Germany

To the Gemeinsamer Bundesausschuss (G-BA)

On behalf of the FH Europe Foundation, we would like to express our profound concern and disappointment regarding the recent decision on ANGPTL3 inhibitor (Evinacumab) for patients with **homozygous familial hypercholesterolaemia** (HoFH) aged 12 years and older in Germany.

The FH Europe Foundation is the first and the only international network of patient organisations, which works in close collaboration with the leading scientific societies and health experts, advocates on behalf of individuals and families affected with familial lipid disorders: heterozygous and homozygous FH (HeFH and HoFH), elevated lipoprotein (a) [Lp(a)], and Familial Chylomicronaemia Syndrome (FCS).

As the leading voice of people living with HoFH, we urge G-BA to consider available scientific evidence in the context of the **genetic cause of HoFH** and the **quality of life** of individuals with this rare and severe disorder and their relatives, while ensuring German citizens' right to health and the best possible **personalised care** in **prevention of cardiovascular diseases (CVD)**. We wish to bring to your attention also the **patient safety** and **health economic** arguments while comparing Evinacumab with other available therapies used in the review process as a comparator for the management of HoFH.

We wish to emphasise that FH Europe Foundation is **an independent, apolitical organisation**, representing the best interest of patients with HoFH. This statement is based on available evidence from scientific research and patient and caregiver lived experiences and is **produced in collaboration with international medical experts representing the European Atherosclerosis Society (EAS), heath technology assessment (HTA) experts and HoFH Patient Ambassadors**. It is being issued in the absence of a dedicated HoFH patient organisation in Germany.

HoFH is an exceptionally **severe and rare genetic disorder** characterized by extremely high levels of low-density lipoprotein (LDL) cholesterol due to mutations in specific genes from birth[1]. **HoFH is inherited in an autosomal dominant manner, which means that an individual receives two mutated genes, one from each biological parent with HeFH.** This is different from

[1] DOI: 10.1093/eurheartj/ehad197

the more common heterozygous FH (HeFH), where only one mutated gene is inherited from one parent. The condition arises from mutations in genes that are crucial for the metabolism of LDL cholesterol. The most common mutations occur in the LDL receptor (*LDLR*) gene, but mutations in other genes like apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) can also cause HoFH.

HoFH significantly increases the risk of premature CVD, incl. atherosclerosis, heart attacks and even death in the first decade of life. Undiagnosed and untreated, HoFH leads to life-threatening consequences already in the first decade of life[2]. Patients with HoFH often have limited therapeutic options, which are targeted and effective as per the specifics of the underlaying genetic cause. Therefore, the efficacy of traditional lipid-lowering therapies is frequently insufficient and need to be accompanied with more aggressive therapeutical approaches such as LDL-apheresis, that diminish the quality of life of patients and families / caregivers. Even LDL-apheresis, considered as rescue therapy, despite its efficacy in delaying the incidence of cardiovascular disease, does not resolve the extremely high atherosclerotic burden associated with HoFH (one patient out of two on LDL-apheresis still experiences a CVD event by the age of 30).[3]

Furthermore, HoFH negatively impacts on the quality of life, physical disability, genetic discrimination, social exclusion and stigmatisation. This hereditary disorder not only reduces life expectancy but also places a substantial burden on daily living. Patients and their families grapple with strict dietary restrictions and frequent medical appointments, which take a toll on their economic well-being. Thus, apart from the health system burden, it supposes a non-deniable societal impact for both patients and families. The invasive treatments, such as apheresis, despite the quality of our healthcare services and their protocols, carry a high risk of infections as it involved manipulating the blood outside the body, monitoring of the access site for bleeding and bruising as well as blood pressure fluctuations is only some of the considerations with this treatment. It is important to recognise that apheresis is not commonly available, forcing patients and families to travel to centres far away from their homes. Additionally, frequent apheresis sessions lasting four or more hours lead to missed school days, denying affected individuals further educational and job opportunities, missed workdays that has an impact on the individual's economic status as well as leaving them feeling overwhelmed. In certain cultures, and religions, HoFH exacerbates gender inequalities and affects deeply personal aspects of life, including marriage and family planning. The psychological impact is profound, with many experiencing anxiety and stress related to their health and future. The aforementioned circumstances exacerbate the societal impact and quality of life reduction of the affected population and their families.

HoFH patients with 2 null LDLR mutations or with 1 null and 1 defective LDLR mutations are at the highest risk. The term "null LDLR" refers to a type of mutation in the LDL receptor (*LDLR*) gene that results in the lack of LDL receptor, which is responsible for clearing LDL cholesterol from the bloodstream. Null *LDLR* mutations are considered the most severe form of genetic alteration in FH because they lead to a complete loss of function of the LDL receptor. Individuals with null/null *LDLR* mutations typically have higher LDL cholesterol levels and a greater risk for coronary artery disease (CAD), including premature CAD, compared to those

[2] DOI: 10.1016/S0140-6736(21)02001-8
[3] https://doi.org/10.1016/S2352-4642(21)00095-X

with defective (but not null) LDLR mutations. The presence of at least one null mutation is associated with a two-fold increase in the risk of major cardiovascular events compared with those with 2 defective LDLR mutations, independently from LDL cholesterol levels and other traditional cardiovascular risk factors. Individuals with null/null and null/defective LDLR mutations, require targeted, aggressive cholesterol-lowering therapies, which work independently of the LDLR pathway.

Evinacumab, in contrast to other currently available therapies, targets angiopoietin-like protein 3 (ANGPTL3), which inhibits lipoprotein lipase (LPL) and endothelial lipase (EL), enzymes that are crucial for the metabolism of triglycerides and phospholipids in very low-density lipoproteins (VLDLs). By inhibiting ANGPTL3, Evinacumab increases the activity of LPL and EL, leading to a reduction in VLDLs and subsequently LDL-C levels. In other words, for HoFH patients with LDLR null/null and null/defective alleles, traditional LDL-C lowering therapies like statins or PCSK9 inhibitors that are depended on LDLR pathway, are less effective because they rely on the presence of functional LDL receptors to remove LDL-C from the blood. If LDLR activity is less than 2% these traditional therapies do not work at all.

Recent data on Evinacumab have shown not only a significant efficacy in terms of LDL-cholesterol lowering in HoFH, but also a reduction of the incidence of cardiovascular events over time, a non-surrogated outcome.[4]

Finally, we would like to address the long term follow up and efficacy concerns, based on the available evidence. In a study with long-term follow-up, adults and adolescent HoFH patients showed a significant drop in LDL-C levels after 24 weeks, which was maintained after 48 weeks.[5] In children aged 5-11 with HoFH on optimized lipid-lowering therapy, including apheresis, Evinacumab reduced LDL-C by almost half at 48 weeks and persisted at 72 weeks, demonstrating long-term efficacy.[6] For adolescents with HoFH, also substantial reductions in uncalcified plaques were observed, allowing them to decrease their apheresis frequency from weekly to once every four weeks.[7]

As a collective of patient advocates and health care and policy experts, we are concerned that the decision to compare ANGPTL3 inhibitor to apheresis and PCSK9 inhibitors, fails to recognise the benefits the therapy offers to patients with unmet needs, denying them the only viable solution to achieve further LDL-C reductions, which is critical in preventing cardiovascular events and improving quality of life. Furthermore, PCSK9 inhibitors can not be put at the same treatment line as current consensus statements of EAS establishes. In accordance with that statement Evinacumab should be used when PCSK9 inhibitors failed to achieve targeted goals.

We believe that every patient deserves access to the best possible, personalised treatment options. Given the gravity of HoFH and the limited effective and appropriate innovative treatment options available in Germany, we urge the G-BA to reassess this decision and to prioritize the health and well-being of patients with HoFH in the country.

[4] https://doi.org/10.1161/ATVBAHA.123.320609
[5] https://doi.org/10.1093/eurheartj/ehae325
[6] Poster presentation at Japanese Atherosclerosis Society 2024; submitted for publication (Wiegman et al)
[7] https://doi.org/10.1016/j.atherosclerosis.2021.04.014

We stand together, ready to engage in constructive dialogue to ensure that the needs of HoFH patients are adequately addressed.

Thank you for your attention to this critical matter.

Sincerely,

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