Evinacumab (homozygous familial hypercholesterolaemia; adults and adolescents 12 years and older)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Evinacumab (homozygote familiäre Hypercholesterinämie, Erwachsene und Jugendliche ab 12 Jahre) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASCVD	atherosclerotic cardiovascular diseases
CTCAE	Common Terminology Criteria for Adverse Events
EAS	European Artherosclerosis Society
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HoFH	homozygous familial hypercholesterolemia
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	Intention to treat
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug evinacumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 10 January 2024.

Research question

The aim of this report is to assess the added benefit of evinacumab as an adjuvant therapy to diet and other lipid-lowering therapies compared to the appropriate comparator therapy (ACT) in adults and adolescents aged 12 years and older with homozygous familial hypercholesterolemia (HoFH) in whom dietary and drug options for lipid lowering have been exhausted

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of evinacumab

Therapeutic indication	**ACT**[a]
Adults and adolescents aged 12 years and older with HoFH in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[b] or LDL apheresis[c] (as "last resort" in refractory disease) possibly with concomitant lipid-lowering drug treatment
a. Presented is the respective ACT specified by the G-BA. b. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive must be observed. c. The G-BA guideline on examination and treatment methods provided under statutory health insurance must be taken into account with regard to performing outpatient apheresis as extracorporeal haemotherapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein	

In Module 3 A of the full dossier assessment, the company deviates in wording from the G-BA's ACT and names a maximum tolerated lipid-lowering therapy of physician's choice, taking into account statins, ezetimibe, evolocumab and low-density lipoprotein(LDL) apheresis as the ACT. The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company's deviation from the ACT specified by the G-BA will not be further commented on below, as the company did not present any suitable data for the benefit assessment – neither versus a comparator therapy specified by the company nor versus the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 12 months were used for the derivation of the added benefit.

Results

The check of the information retrieval revealed no relevant randomized controlled trial (RCT) for the assessment of the added benefit of evinacumab compared with the ACT. By contrast, the company included the RCT ELIPSE-HoFH study for direct comparison. In addition, the company identified the single-arm study R1500-CL-1719 in its information retrieval on further studies with evinacumab. Both studies are not suitable for deriving conclusions on the added benefit of evinacumab in comparison with the ACT. The studies ELIPSE-HoFH and R1500-CL-1719 are described below and the reasons for their exclusion are explained in each case.

Studies included by the company

ELIPSE-HoFH

The ELIPSE-HoFH study (R1500-CL-1629) is a randomized, double-blind study comparing evinacumab with placebo, in each case in combination with a maximum tolerated lipid-lowering therapy.

Patients aged ≥ 12 years with HoFH were included. For screening, patients had to have a low-density lipoprotein cholesterol (LDL-C) value ≥ 70 mg/dL. In addition, patients should be on a maximum tolerated statin, ezetimibe and a Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitor (evolocumab or alirocumab), unless there was a documented history of tolerability problems, little or no response to therapy or other documented reasons. The maximum tolerated lipid-lowering therapy could also include LDL apheresis or other lipid-lowering drugs and should be steady for at least 4 weeks for screening. Furthermore, patients were required to adhere to a steady, low-fat or heart-healthy diet and a steady training programme for the duration of the study.

The ELIPSE-HoFH study included a total of 65 patients, randomized in a 2:1 ratio to treatment with either evinacumab (N = 43) or placebo (N = 22).

The ELIPSE-HoFH study consists of 2 treatment phases. In the 24-week double-blind treatment period, patients were treated with either evinacumab or placebo. In the following, 24-week open-label treatment period all patients were exclusively treated with evinacumab. Evinacumab was dosed in accordance with the Summary of Product Characteristics (SPC). In addition, patients were required to continue steady lipid-lowering therapy throughout the study period from screening to the end of the open-label treatment period. After completing the open treatment period, patients had the option to continue treatment with evinacumab in the open-label single-arm study R1500-CL-1719.

The primary outcome in the ELIPSE-HoFH study was the percentage change in LDL-C levels between baseline and week 24 (double-blind treatment period).

R1500-CL-1719

The R1500-CL-1719 study is a single-arm, open-label study to assess the long-term safety and efficacy of evinacumab. The study included patients who had either completed the ELIPSE-HoFH study or the R1500-CL-1331 study and had therefore already been treated with evinacumab, or evinacumab-naïve patients, each ≥ 12 years with HoFH. Patients continued a maximum tolerated lipid-lowering therapy in addition to treatment with evinacumab. In addition, all patients were required to maintain a heart-healthy diet and exercise programme throughout the duration of the study. A total of 116 adult patients (≥ 18 years) and 14 adolescent patients (< 18 years) were included in R1500-CL-1719 study.

Treatment-related adverse events (AEs) were the primary outcome in study R1500-CL-1719.

The single-arm study R1500-CL-1719 is not suitable for the assessment of added benefit of evinacumab compared to the ACT as it does not provide comparative data. Therefore, the R1500-CL-1719 study is not discussed any further hereinafter.

Unsuitability of the ELIPSE-HoFH study presented by the company for the benefit assessment

The ELIPSE-HoFH study is unsuitable for deriving any conclusions on the added benefit of evinacumab in comparison with the ACT. Primary reasons for its unsuitability are the following:

- Too short comparative study duration of 24 weeks (minimum study duration for the therapeutic indication of hypercholesterolaemia ≥ 12 months)
- Uncertainty as to whether the drug options for lipid lowering were actually exhausted in pretreatment for a relevant proportion of the study population (> 20% of the study population was not treated with ezetimibe due to lack of availability)
- Lack of ACT implementation: At least 36.3% of patients in the comparator arm were not treated according to the ACT defined by the G-BA, as they received neither evolocumab nor LDL apheresis. Furthermore, it is questionable whether for patients treated with evolocumab, additional LDL apheresis was an option or whether for patients receiving LDL apheresis, an adjustment of the LDL apheresis frequency was still an option. Thus, the presented study results (outcome: proportion of patients meeting the criteria of the European Atherosclerosis Society (EAS) for the use of LDL apheresis) illustrate that LDL apheresis would have been particularly indicated for the majority of the study population.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of evinacumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of the probability and extent of added benefit of evinacumab.

Table 3: Evinacumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults and adolescents aged 12 years and older with HoFH in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[b] or LDL apheresis[c] (as "last resort" in refractory disease) possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive must be observed.
c. The G-BA guideline on examination and treatment methods provided under statutory health insurance must be taken into account with regard to performing outpatient apheresis as extracorporeal haemotherapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit of evinacumab as an adjuvant therapy to diet and other lipid-lowering therapies compared to the ACT in adults and adolescents aged 12 years and older with homozygous familial hypercholesterolemia (HoFH) in whom dietary and drug options for lipid lowering have been exhausted

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of evinacumab

Therapeutic indication	**ACT**[a]
Adults and adolescents aged 12 years and older with HoFH in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[b] or LDL apheresis[c] (as "last resort" in refractory disease) possibly with concomitant lipid-lowering drug treatment

a. Presented is the respective ACT specified by the G-BA.
b. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive [3] must be observed.
c. The G-BA guideline on examination and treatment methods provided under statutory health insurance [4] must be taken into account with regard to performing outpatient apheresis as extracorporeal haemotherapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein

On receipt of the dossier, the G-BA adjusted the ACT on 6 February 2024 in as presented in Table 4 [5]. Following this adjustment, the originally defined research question 1 is no longer required: Adults and adolescents aged 12 years and older with HoFH in whom dietary and drug options for lipid lowering have been exhausted. According to the G-BA's adjustment (which refers to the company's reasoning according to Module 3 A), this patient population is not part of the target population of evinacumab and thus not part of this benefit assessment. The original research question 2 – Adults and adolescents aged 12 years and older with HoFH in whom dietary and drug options for lipid lowering have been exhausted – remains unaffected by the adjustment. The present benefit assessment is conducted according to the adjusted ACT for adults and adolescents aged 12 years and older with HoFH in whom dietary and drug options for lipid lowering have been exhausted.

In Module 3 A of the full dossier assessment, the company deviates in wording from the G-BA's ACT and names a maximum tolerated lipid-lowering therapy of physician’s choice, taking into account statins, ezetimibe, evolocumab and low-density lipoprotein(LDL) apheresis as the ACT. The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company’s deviation from the ACT specified by the G-BA will not be further commented on below because the company did not present any suitable data for the benefit

assessment – neither compared to a comparator therapy designated by the company nor compared to the ACT specified by the G-BA (for explanation see Chapter I 3).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 12 months were used for the derivation of the added benefit. This deviates from the company's inclusion criteria, which specified a minimum duration of 24 weeks.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on evinacumab (status: 15 November 2023)
- bibliographical literature search on evinacumab (last search on 15 November 2023)
- search in trial registries/trial results databases for studies on evinacumab (last search on 13 November 2023)
- search on the G-BA website for evinacumab (last search on 14 November 2023)

To check the completeness of the study pool:

- search in trial registries for studies on evinacumab (last search on 24 January 2024); for search strategies, see I Appendix A of the full dossier assessment

The check found no relevant RCTs for assessing the added benefit of evinacumab in comparison with the ACT. On the other hand, the company included the RCT ELIPSE-HoFH for direct comparison [6-11]. This RCT was unsuitable to derive conclusions on the added benefit of evinacumab in comparison with the ACT. Primary reasons for its unsuitability are the following:

- Too short comparative study duration of 24 weeks (minimum study duration for the therapeutic indication of hypercholesterolaemia ≥ 12 months)
- Uncertainty as to whether the drug options for lipid lowering were actually exhausted in pretreatment for a relevant proportion of the study population
- Lack of ACT implementation

Furthermore, during its information retrieval activities for further investigations with evinacumab, the company identified the single-arm study R1500-CL-1719 [12]. The company conducted no information retrieval on further investigations with the ACT. The company included the study R1500-CL-1719 in the study pool of further investigations, presented the study results in Module 4 A, and considered this study in the assessment of the additional benefit supporting the results of the RCT ELIPSE-HoFH. The single-arm study R1500-CL-1719 is not suitable for the assessment of added benefit of evinacumab compared to the ACT as it does not provide comparative data.

The studies ELIPSE-HoFH and R1500-CL-1719 are described below and the reasons for their exclusion are explained in each case. The characterization of the ELIPSE-HoFH study is additionally presented in I Appendix B of the full dossier assessment.

Studies included by the company

ELIPSE-HoFH

The ELIPSE-HoFH study (R1500-CL-1629) is a randomized, double-blind study comparing evinacumab with placebo, in each case in combination with a maximum tolerated lipid-lowering therapy.

Patients aged ≥ 12 years with HoFH were included. The diagnosis of HoFH was based on genetic or clinical criteria (see Table 6 of the full dossier assessment). For screening, patients had to have a low-density lipoprotein cholesterol (LDL-C) value ≥ 70 mg/dL. In addition, patients should be on a maximum tolerated statin, ezetimibe and a Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitor (evolocumab or alirocumab), unless there was a documented history of tolerability problems, little or no response to therapy or other documented reasons. The maximum tolerated lipid-lowering therapy could also include LDL apheresis or other lipid-lowering drugs and should be steady for at least 4 weeks for screening (PCSK9 inhibitors: 8 weeks, LDL apheresis: 8 weeks in a 7-day [± 1 day] or 14-day [± 2 days] regimen). If lipid-lowering therapy (including LDL apheresis parameters) had to be steadied before screening or the diagnosis of HoFH had to be confirmed by genotyping, patients were included in a run-in phase of up to 8 weeks. Furthermore, patients were required to adhere to a steady, low-fat or heart-healthy diet and a steady training programme for the duration of the study.

The ELIPSE-HoFH study included a total of 65 patients, randomized in a 2:1 ratio to treatment with either evinacumab (N = 43) or placebo (N = 22). Including 1 patient < 18 years of age per study arm. Stratification was based on LDL apheresis treatment status (yes vs. no) and geographical region (Japan vs. rest of the world).

The ELIPSE-HoFH study consists of 2 treatment phases. In the 24-week double-blind treatment period, patients were treated with either evinacumab or placebo. In the following, 24-week open-label treatment period all patients were exclusively treated with evinacumab.

Evinacumab dosage was administered in line with the SPC [13] (see Table 7 of the full dossier assessment). In addition, patients were required to continue steady lipid-lowering therapy throughout the study period from screening to the end of the open-label treatment period.

After completing the open-label treatment period, patients had the option to continue treatment with evinacumab in the open-label single-arm study R1500-CL-1719 (see section on study R1500-CL-1719 below). Patients who did not consent to participate in the R1500-CL-1719 study or who discontinued study treatment prematurely took part in a 24-week follow-up observation phase.

The primary outcome in the ELIPSE-HoFH study was the percentage change in LDL-C levels between baseline and week 24 (double-blind treatment period). Further outcomes were

recorded according to information in Module 4 A in the categories of morbidity and side effects.

Subpopulations presented by the company:

In order to address the transferability of the study results to the German healthcare context, the company additionally presented sensitivity analyses (post hoc for all efficacy outcomes) for the following subpopulations in Module 4 A:

- Intention to treat (ITT) population excluding patients treated with probucol and/or lomitapide treatment
- ITT population excluding patients treated with probucol and/or lomitapide and/or alirocumab

The company did not provide information on lipid-lowering primary and concomitant therapy for these subpopulations. The company's approach is not commented on further, as the ELIPSE-HoFH study is not suitable for the benefit assessment (see the following section "Unsuitability of the ELIPSE-HoFH study presented by the company for the benefit assessment"). In the following reasoning, data for the total population of the ELIPSE-HoFH study are used.

R1500-CL-1719

The R1500-CL-1719 study is a single-arm, open-label study to assess the long-term safety and efficacy of evinacumab. The study included patients who had either completed the ELIPSE-HoFH study or the R1500-CL-1331 study and had therefore already been treated with evinacumab (referred to as the Continue Evinacumab group in Module 4 A), or evinacumab-naïve patients (referred to as the New Evinacumab group in Module 4 A), each ≥ 12 years with HoFH. The diagnosis of HoFH was based on genetic or clinical criteria and corresponded to the diagnostic criteria in the ELIPSE-HoFH study (see Table 6 of the full dossier assessment).

Patients continued a maximum tolerated lipid-lowering therapy in addition to treatment with evinacumab. This could include a maximum tolerated statin, ezetimibe, PCSK9 inhibitors, or other lipid-lowering therapies including LDL apheresis. Patients who received lipid-lowering therapy that has been shown to reduce the risk of atherosclerotic cardiovascular diseases (ASCVD), e.g. statins, ezetimibe, PCSK9 inhibitors, should strive to maintain this concomitant therapy steady throughout the entire study duration. Other lipid-lowering therapies (e.g. LDL-apheresis, lomitapide) could be adjusted after week 24 based on the LDL-C value, cardiovascular risk factors, and assessment by the investigator. Patients who have been treated with evinacumab in previous studies were required to steadily continue their lipid-lowering therapy, including LDL apheresis (if applicable), without any adjustments for the

duration of the study. In addition, all patients were required to maintain a heart-healthy diet and exercise programme throughout the duration of the study.

A total of 116 adult patients (≥ 18 years) and 14 adolescent patients (< 18 years) were included in R1500-CL-1719 study. In Module 4 A, data are available for study R1500-CL-1719 up to week 120. Treatment-related AEs were the primary outcome in study R1500-CL-1719. Further outcomes were recorded according to information in Module 4 A in the categories of morbidity and side effects.

The single-arm study R1500-CL-1719 is not suitable for the assessment of added benefit of evinacumab compared to the ACT as it does not provide comparative data. Therefore, the R1500-CL-1719 study is not discussed any further hereinafter.

Unsuitability of the ELIPSE-HoFH study presented by the company for the benefit assessment

Duration of the ELIPSE-HoFH study not sufficient

In Module 4 A, the company defined a minimum study duration of 24 weeks as an inclusion criterion, and it included the ELIPSE-HoFH study for assessing the added benefit of evinacumab in comparison with the ACT. Comparative data for a period of 24 weeks is available based on the double-blind treatment period of the ELIPSE-HoFH study.

The approach of the company is not appropriate. Similar to previous benefit assessments in the therapeutic indication of hypercholesterolaemia [14-19], a minimum study duration of 12 months is considered necessary. Evinacumab serves as long-term treatment of a chronic disease with the primary goal of lowering LDL-C values to reduce cardiovascular risks. Assessing the long-term effects of evinacumab on patient-relevant outcomes therefore requires a longer observation period than the 24-week double-blind treatment period in the ELIPSE-HoFH study. In Module 4 A, the company referred to the long-term efficacy and safety of evinacumab on the basis of the results of the open-label treatment period of the ELIPSE-HoFH study and the results of the R1500-CL-1719 study, but these study results are not suitable for the assessment of the added benefit of evinacumab in comparison with the ACT in the context of the present benefit assessment, as they do not provide any comparative data.

Prior drug therapy of the study population

In the present therapeutic indication, the therapeutic goal is to reduce the LDL-C value to < 70 mg/dL in adults and < 115 mg/dL in children and adolescents, provided there are no ASCVD risk factors (e.g. diabetes mellitus). If additional ASCVD risk factors or proven ASCVD are present, an LDL-C value < 55 mg/dL should be aimed for in adults. A lower LDL value should also be aimed for in children and adolescents with proven ASCVD. The treatment algorithm

provides for treatment with a high-dose statin and ezetimibe at the time of diagnosis. If the LDL-C target values are not reached within 8 weeks, additional treatment with a PCSK9 inhibitor should be given. If treatment response is poor (< 15% LDL-C reduction after 1-2 doses), physicians should consider discontinuing PCSK9 inhibitors. If the LDL-C target value is still not achieved, the subsequent therapeutic options include LDL apheresis and/or LDL receptor-independent drugs, such as evinacumab [20].

The present research question of the G-BA concerns patients aged 12 years and older with HoFH in whom dietary and drug options for lipid lowering have been exhausted. In the ELIPSE-HoFH study, the prior lipid-lowering drug therapy which was continued steadily during the course of the study and thus also represents the concomitant therapy in the study, included statins, ezetimibe and PCSK9 inhibitors. Detailed information on the lipid-lowering therapy in the ELIPSE-HoFH study is presented in Table 8 of the full dossier assessment. At baseline, 93.8 % ([41 + 20]/65) of the study population were treated with a statin, including 76.9 % ([34 + 16]/65) with a high-dose statin. Prior to lipid-lowering therapy, 89.2% ([39 + 19]/65) of the study population received a high-dose statin, 86.2% ([37 + 19]/65) were treated with a maximum tolerated statin dose. In addition, 75.4% ([33 + 16]/65) of patients were treated with ezetimibe and 76.9% ([34 + 16]/65) of patients were treated with a PCSK9 inhibitor at baseline. Treatment with a PCSK9 inhibitor included the drugs evolocumab (35.4% [[17+6]/65] of patients) and alirocumab (41.5% [[17+10]/65] of patients), whereby alirocumab is not approved for the treatment of HoFH in Germany [21]. The reasons why high-dose statin therapy or lipid-lowering therapy with a PCSK9 inhibitor was not an option for all patients included muscular side effects in the case of statins and the lack of efficacy of PCSK9 inhibitors in pretreatment. These reasons are plausible, as statin-associated muscle symptoms (usually subjective myalgia) are among the most common side effects of statins [22], and the effect of PCSK9 inhibitors is LDL receptor-dependent [20]. The most common reason why ezetimibe was not suitable for all patients as part of lipid-lowering treatment was the lack of availability (more detailed information is not available in the study documents). Taking into account the German healthcare context, the justification of the lack of availability is insufficient, as ezetimibe in combination with a statin and a diet is approved for patients with HoFH in Germany [23] and is therefore available as a relevant drug therapy option. Based on the available information, it therefore remains unclear whether ezetimibe could have been considered as a lipid-lowering drug option for > 20% of the study population.

Overall, the majority of the study population of the RCT ELIPSE-HoFH was heavily pretreated: 63% of the study population was treated with 3 lipid-lowering drugs and 98.5% ([42 + 22]/65) of the study population was treated with a maximum tolerated lipid-lowering therapy according to the investigator's assessment. However, without specifying any reasons other than the lack of availability of ezetimibe, it remains unclear whether all drug options for lipid lowering have actually been exhausted for a relevant proportion of the study population.

ACT not implemented

In the present therapeutic indication, the G-BA has defined evolocumab and/or LDL apheresis (as "last resort" in refractory disease) possibly with concomitant lipid-lowering therapy as ACT. In the ELIPSE-HoFH study, 27.3% of patients in the comparator arm were treated with evolocumab and 36.4% of patients with LDL apheresis (see Table 8 of the full dossier assessment). Consequently, at least 36.3% of patients in the comparator arm were not treated in accordance with the G-BA's ACT. Accordingly, the ACT was not adequately implemented for a relevant proportion of patients in the comparator arm.

In addition, the study documents do not contain any information on the combination treatment with evolocumab and LDL apheresis. It is therefore unclear how many patients in the comparator arm were treated with both evolocumab and LDL apheresis at the start of the study and how many patients in the comparator arm were only treated with evolocumab, although LDL apheresis would have been indicated as the next treatment option. Overall, it therefore remains unclear whether additional LDL apheresis would have been an option for 27.3% of patients in the comparator arm who were treated with evolocumab at the start of the study.

According to the guideline recommendation, LDL apheresis is essential for the treatment of HoFH in both children and adults and is usually performed in a bi-weekly or even weekly regimen [20]. The German Society of Nephrology recommends that LDL apheresis should be started in childhood at the time of diagnosis of HoFH [24]. In the ELIPSE-HoFH study, 36.4% of patients in the comparator arm were treated with LDL apheresis. Among them, 13.6% of patients with a bi-weekly LDL apheresis frequency. For these patients, it is unclear whether adjusting the LDL apheresis frequency to a weekly regiment was still an option to reduce the LDL-C level.

Furthermore, patients in the ELIPSE-HoFH were required to maintain a steady lipid-lowering therapy and a steady LDL apheresis regimen (if applicable; weekly or bi-weekly) for the entire duration of the study, from screening to the end of the study. Furthermore, investigators were blinded to all lipid values and were not supposed to attempt to determine them independently. Particularly the LDL-C value, however, represents a relevant lipid parameter for treatment management in the present therapeutic indication, which means that target value-oriented treatment would not even have been possible in the ELIPSE-HoFH study. The results on the percentage change in LDL-C levels between baseline and week 24, however, show that the LDL-C value in the comparator arm remains almost unchanged over the entire course of the study, while in the intervention arm, a reduction in LDL-C levels is achieved after starting treatment with evinacumab (see Figure 1). Given that the baseline LDL-C values were outside the target range (mean 259.5 mg/dL in the evinacumab arm vs. 246.5 mg/dL in the placebo arm), however, the majority of participants in the comparator arm would have been indicated for optimization of lipid-lowering therapy.

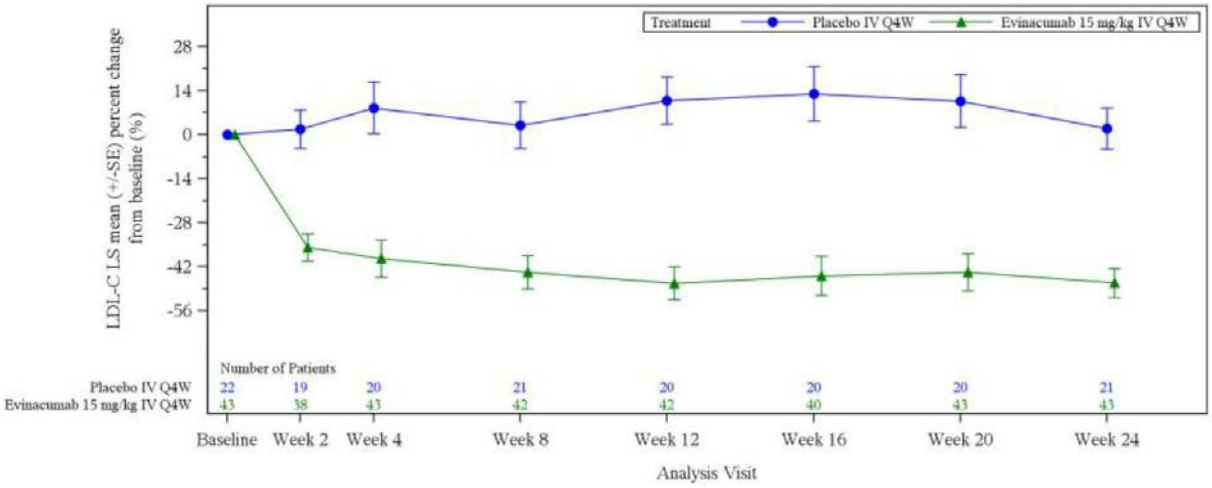

Figure 1: Percentage change in LDL-C from baseline to week 24 of the ELIPSE-HoFH study

The study results for the outcome "Proportion of patients meeting, among other criteria, the European Atherosclerosis Society[4] (EAS) [20] criteria for LDL apheresis application" also show that in the ELIPSE-HoFH study, significantly more patients in the comparator arm met the criteria for LDL apheresis. According to the EAS criteria, an LDL apheresis was indicated for 79.1% (evinacumab arm) or 100% (placebo arm) of the patients by week 24. However, patients in the ELIPSE-HoFH study continued steady lipid-lowering therapy without any adjustment over the course of the study despite not reaching the LDL-C target values. However, the results described show that it would have been necessary to take further measures to reduce LDL-C levels during the course of the study, such as in particular starting treatment with LDL apheresis in patients who had not yet received LDL apheresis at baseline. Accordingly, it does not seem appropriate that only about 1/3 of the patients in the comparator arm were treated with LDL apheresis – the ACT was therefore not adequately implemented.

In summary, at least 36.3% of patients in the comparator arm of the ELIPSE-HoFH study were not treated according to the ACT defined by the G-BA, as they received neither evolocumab nor LDL apheresis. Furthermore, it is questionable whether for patients treated with evolocumab, additional LDL apheresis was an option or whether for patients receiving LDL apheresis, an adjustment of the LDL apheresis frequency was still an option. These study results illustrate that LDL apheresis would have been indicated for the majority of the study population. Overall, the ELIPSE-HoFH study did not adequately implement the ACT defined by the G-BA.

[4]Primary prevention: LDL-C > 70 mg/dL in the absence of additional risk factors for ASCVD exist; secondary prevention: LDL-C > 55 mg/dL in the presence of additional risk factors or already manifest ASCVD

I 4 Results on added benefit

There are no suitable data available for the assessment of the added benefit of evinacumab as an adjuvant therapy to diet and other lipid-lowering therapies compared to the ACT in adults and adolescents aged 12 years and older with HoFH in whom dietary and drug options for lipid lowering have been exhausted. There is no hint of an added benefit of evinacumab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of evinacumab in comparison with the ACT is summarized in Table 5.

Table 5: Evinacumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults and adolescents aged 12 years and older with HoFH in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[b] or LDL apheresis[c] (as "last resort" in refractory disease) possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive [3] must be observed.
c. The G-BA guideline on examination and treatment methods provided under statutory health insurance [4] must be taken into account with regard to performing outpatient apheresis as extracorporeal haemotherapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein

The assessment described above deviates from that by the company, which derived an indication of major added benefit.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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