IQWiG Reports – Commission No. A21-171

Evolocumab (familial hypercholesterolaemia in children and adolescents aged 10 years and over) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Evolocumab (familiäre Hypercholesterinämie bei Kindern und Jugendlichen ab 10 Jahren) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 March 2022). 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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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Manfred Gogol, Medical University of Hanover, Clinic for Trauma Surgery, Geriatric Trauma Centre, Hanover, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

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

IQWiG employees involved in the dossier assessment

- Selver Altin
- Wiebke Hoffmann-Eßer
- Claudia Kapp
- Stefan Kobza
- Philip Kranz
- Jona Lilienthal
- Katrin Nink
- Sabine Ostlender

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HeFH	heterozygous familial hypercholesterolaemia
HoFH	homozygous familial hypercholesterolaemia
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDL-C	low-density lipoprotein cholesterol
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug evolocumab. 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 22 December 2021.

Research question

The objective of this report is to assess the added benefit of evolocumab:

- as an adjunct to diet and, if necessary, in combination with other lipid-lowering therapies in comparison with the appropriate comparator therapy (ACT) in patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia (HeFH) and
- in combination with other lipid-lowering therapies in comparison with the ACT in patients aged 10 to 11 years with homozygous familial hypercholesterolaemia (HoFH).

The research questions shown in Table 2 were derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of evolocumab

Research question	Therapeutic indication	ACT[a]
1	Children and adolescents with HeFH[b] aged 10 to 17 years in whom dietary and drug options for lipid lowering have not been exhausted[c]	Maximum tolerated drug treatment according to physician's choice[d], selecting from statins, cholesterol absorption inhibitors, and anion exchange resins
2	Children and adolescents with HeFH[b] aged 10 to 17 years in whom dietary and drug options for lipid lowering have been exhausted[c]	LDL apheresis[e] (as a last resort in refractory disease), if necessary with concomitant lipid-lowering drug treatment
3	Children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have not been exhausted[c]	Maximum tolerated drug treatment according to physician's choice[d], selecting from statins, cholesterol absorption inhibitors, and anion exchange resins
4	Children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have been exhausted[c]	LDL apheresis[e] (as a last resort in refractory disease), if necessary with concomitant lipid-lowering drug treatment

a. Presented is the respective ACT specified by the G-BA.
b. In the absence of statin intolerance or contraindication, evolocumab is, according to the approval statement, indicated only for patients with HeFH who do not reach LDL-C targets on the maximum tolerated statin dose.
c. According to the stipulations specified in the "Prescribing limitations for prescription-only lipid-lowering drugs" in Appendix III of the German Pharmaceutical Directive.
d. As noted by the G-BA, maximum tolerated drug therapy can also comprise a combination of different drug classes; the treatment regimens used in the intervention and comparator arms are assumed to be similar. Furthermore, the continuation of inadequate therapy (including in terms of dosage) over the course of the study does not represent an implementation of the ACT unless the maximum tolerated drug therapy has already been exhausted for a given patient. A single-comparator study is typically insufficient for implementing treatment according to physician's choice in a directly comparative study.
e. 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; HeFH: heterozygous familial hypercholesterolaemia; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein; LDL-C: LDL cholesterol

The company followed the ACT specified by the G-BA for research questions 2 and 4.

For research questions 1 and 3, the company chose the ACT designated by the G-BA, but it followed this ACT only to some extent, concluding that individually optimized therapy at a stable dose is an adequate implementation of the ACT. Overall, the company did not appropriately justify its deviation from the ACT specified by the G-BA. This is explained below. For all research questions, the present benefit assessment was therefore conducted in comparison with 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. Randomized controlled trials (RCTs) with a minimum duration of 12 months were used for deriving added benefit.

Inappropriate deviation by the company from the G-BA's specification of the ACT for research questions 1 and 3

The company reports that neither the associated Summaries of Product Characteristics (SPCs) nor the guidelines clearly define treatment escalation for familial hypercholesterolaemia in children, and therefore, no unambiguous criteria for "maximum tolerated" therapy are available for this patient group. The company stresses that the decisive criterion for a child's drug therapy to be deemed the maximum tolerated drug therapy is the physician's assessment or decision on the individual patient level and that the maximum dose tolerated by an individual patient is not necessarily equal to a drug's maximum dose. Therefore, the company argues that a stable regimen of individually optimized therapy constitutes an adequate implementation of the ACT specified by the G-BA.

The company's justification of its deviation from the ACT is not appropriate. While the company is correct in that the maximum tolerated dose cannot be equated with a drug's approved maximum dose, clear recommendations for treatment escalation based on low-density lipoprotein cholesterol (LDL-C) values exist for the present therapeutic indication. The guidelines do not, however, recommend a stable treatment regimen irrespective of LDL-C targets. Furthermore, the G-BA's comments on the ACT explicitly state that the continuation of an inadequate therapy (including in terms of its dosage) over the course of a study does not represent an implementation of the ACT unless the maximum tolerated drug therapy has been reached for the individual patient.

All in all, the deviation from the ACT specified by the G-BA has therefore not been adequately justified. The present benefit assessment therefore uses the ACT specified by the G-BA for all research questions.

Research question 1: Children and adolescents with HeFH aged 10 to 17 years in whom dietary and drug options for lipid lowering have not been exhausted

Study pool and study design

The check of completeness of the study pool did not reveal any relevant RCT for assessing the added benefit of evolocumab in comparison with the ACT. The company, in contrast, used the 24-week HAUSER RCT. The HAUSER RCT was unsuitable for deriving any conclusions on the added benefit of evolocumab in comparison with the ACT. Below, the HAUSER RCT is described, and the reasoning for its exclusion provided.

HAUSER RCT presented by the company

The HAUSER RCT is a randomized, controlled, double-blind study comparing evolocumab versus placebo, each in combination with low-fat diet and a stable regimen of lipid-lowering therapy.

It enrolled children and adolescents ≥ 10 and ≤ 17 years who had been diagnosed with HeFH. At screening, patients had to have a fasting LDL-C ≥ 130 mg/dL and, prior to screening, been

treated for ≥ 4 weeks with a stable regimen of approved statin therapy which the investigator deemed not to require further intensification.

The HAUSER RCT included a total of 158 patients, randomized in a 2:1 ratio to treatment with either evolocumab (N = 105) or placebo (N = 53). Treatment with evolocumab was in compliance with the specifications of the SPC. Furthermore, patients continued the low-fat diet as well as the stable regimen of lipid-lowering therapy as background therapy during study treatment. HAUSER RCT participants were treated for 24 weeks, and after the end of the study, they were allowed to join the single-arm, open-label HAUSER OLE extension study to continue or, if they previously received placebo, to start evolocumab treatment.

The primary outcome of the HAUSER RCT was change in LDL-C value between study start and Week 24. Further outcomes were surveyed in the morbidity and side effects categories.

Unsuitability of the HAUSER RCT presented by the company for the benefit assessment

The HAUSER RCT is unsuitable for deriving any conclusions on the added benefit of evolocumab in comparison with the ACT. Primary reasons for its unsuitability are the following:

- Short study duration of 24 weeks (≥ 12 months minimum study duration for the therapeutic indication of hypercholesterolaemia)
- Wrong population (it had not been ensured that enrolled patients received prior therapy with their maximum tolerated statin dose in accordance with the evolocumab approval)
- Lack of implementation of the ACT since the study did not allow any adjustments of lipid-lowering therapy to the maximum tolerated drug treatment according to physician's choice over its course even in patients who failed to reach LDL-C targets

Results

No suitable data are available for assessing any added benefit of evolocumab in comparison with the ACT in children and adolescents with HeFH aged 10 to 17 years in whom dietary and drug options for lipid lowering have not been exhausted. This results in no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: Children and adolescents with HeFH aged 10 to 17 years in whom dietary and drug options for lipid lowering have been exhausted

Study pool

Concurring with the company, the check of completeness of the study pool identified no directly comparative study for the present research question.

Results

No data are available for assessing any added benefit of evolocumab in comparison with the ACT for children and adolescents with HeFH aged 10 to 17 years in whom dietary and drug

options for lipid lowering have been exhausted. This results in no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 3: children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have not been exhausted

Study pool

Concurring with the company, the check of completeness of the study pool identified no directly comparative study for the present research question.

In the absence of studies offering a direct comparison, the company conducted an additional information retrieval for further investigations. For the intervention, the company found the single-arm HAUSER-OLE study. The company conducted no information retrieval on the ACT.

The single-arm HAUSER-OLE study was unsuitable for deriving any conclusions on the added benefit of evolocumab in comparison with the ACT because it does not allow a comparison with the ACT.

Results

No suitable data are available for assessing any added benefit of evolocumab in comparison with the ACT for children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have not been exhausted. This results in no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 4: children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have been exhausted

Study pool

Concurring with the company, the check of completeness of the study pool identified no directly comparative study for the present research question. In the absence of studies offering a direct comparison, the company conducted an additional information retrieval for further investigations, but it did not find any relevant studies.

Results

No suitable data are available for assessing any added benefit of evolocumab in comparison with the ACT for children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have been exhausted. This results in no hint of an added benefit of evolocumab 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]

On the basis of the results presented, the probability and extent of added benefit of the drug evolocumab in comparison with the ACT are assessed as follows:

Table 3 presents a summary of the probability and extent of added benefit of evolocumab.

[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].

Table 3: Evolocumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Children and adolescents with HeFH[b] aged 10 to 17 years in whom dietary and drug options for lipid lowering have not been exhausted[c]	Maximum tolerated drug treatment according to physician's choice[d], selecting from statins, cholesterol absorption inhibitors, and anion exchange resins	Added benefit not proven
2	Children and adolescents with HeFH[b] aged 10 to 17 years in whom dietary and drug options for lipid lowering have been exhausted[c]	LDL apheresis[e] (as a last resort in refractory disease), if necessary with concomitant lipid-lowering drug treatment	Added benefit not proven
3	Children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have not been exhausted[c]	Maximum tolerated drug treatment according to physician's choice[d], selecting from statins, cholesterol absorption inhibitors, and anion exchange resins	Added benefit not proven
4	Children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have been exhausted[c]	LDL apheresis[e] (as a last resort in refractory disease), if necessary with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In the absence of statin intolerance or contraindication, evolocumab is indicated, according to approval, only for patients with HeFH who do not reach LDL-C targets on their maximum tolerated statin dose.
c. According to the stipulations specified in the "Prescribing limitations for prescription-only lipid-lowering drugs" in Appendix III of the German Pharmaceutical Directive.
d. As noted by the G-BA, maximum tolerated drug therapy can also comprise a combination of different drug classes; the treatment regimens used in the intervention and comparator arms are assumed to be similar. Furthermore, the continuation of inadequate therapy (including in terms of dosage) over the course of the study does not represent an implementation of the ACT unless the maximum tolerated drug therapy has already been exhausted for a given patient. A single-comparator study is typically insufficient for implementing treatment according to physician's choice in a directly comparative study.
e. 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; HeFH: heterozygous familial hypercholesterolaemia; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein; LDL-C: LDL cholesterol

The G-BA decides on the added benefit.

2.2 Research question

The objective of this report is to assess the added benefit of evolocumab:

- as an adjunct to diet, and possibly in combination with other lipid-lowering therapies in comparison with the ACT in patients with HeFH aged 10 to 17 years and
- in combination with other lipid-lowering therapies in comparison with the ACT in patients with HoFH aged 10 to 11 years.

The research questions shown in Table 4 were derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of evolocumab

Research question	Therapeutic indication	ACT[a]
1	Children and adolescents with HeFH[b] aged 10 to 17 years in whom dietary and drug options for lipid lowering have not been exhausted[c]	Maximum tolerated drug treatment according to physician's choice[d], selecting from statins, cholesterol absorption inhibitors, and anion exchange resins
2	Children and adolescents with HeFH[b] aged 10 to 17 years in whom dietary and drug options for lipid lowering have been exhausted[c]	LDL apheresis[e] (as a last resort in refractory disease), if necessary with concomitant lipid-lowering drug treatment
3	Children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have not been exhausted[c]	Maximum tolerated drug treatment according to physician's choice[d], selecting from statins, cholesterol absorption inhibitors, and anion exchange resins
4	Children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have been exhausted[c]	LDL apheresis[e] (as a last resort in refractory disease), if necessary with concomitant lipid-lowering drug treatment

a. Presented is the respective ACT specified by the G-BA.
b. In the absence of statin intolerance or contraindication, evolocumab is indicated, according to the approval statement, only for patients with HeFH who do not reach LDL-C targets on the maximum tolerated statin dose [3].
c. According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the German Pharmaceutical Directive [4].
d. As noted by the G-BA, maximum tolerated drug therapy can also comprise a combination of different drug classes; the treatment regimens used in the intervention and comparator arms are assumed to be similar. Furthermore, the continuation of inadequate therapy (including in terms of dosage) over the course of the study does not represent an implementation of the ACT unless the maximum tolerated drug therapy has already been exhausted for a given patient. A single-comparator study is typically insufficient for implementing treatment according to physician's choice in a directly comparative study.
e. 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; HeFH: heterozygous familial hypercholesterolaemia; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein; LDL-C: LDL cholesterol

The company followed the ACT specified by the G-BA for research questions 2 and 4.

For research questions 1 and 3, the company chose the ACT designated by the G-BA, but it followed this ACT only to some extent, concluding that individually optimized therapy at a stable dose is an adequate implementation of the ACT. Overall, the company did not appropriately justify its deviation from the ACT specified by the G-BA. The rationale is provided below. For all research questions, the present benefit assessment was therefore conducted in comparison with 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. RCTs with a minimum duration of 12 months were used for deriving added benefit. This deviates from the company's inclusion criteria, which specified a minimum duration of 12 weeks.

Inappropriate deviation by the company from the G-BA's specification of the ACT for research questions 1 and 3

In Modules 3 A and B as well as 4 A and B, the company reports that neither the associated SPCs nor the guidelines clearly define treatment escalation for familial hypercholesterolaemia in children, and therefore, no unambiguous criteria for "maximum tolerated" therapy are available for this patient group. The company stresses that the decisive criterion for a child's drug therapy to be deemed the maximum tolerated drug therapy is the physician's assessment or decision on the patient-by-patient level and that the maximum dose tolerated by an individual patient is not necessarily equal to a drug's maximum dose. Therefore, the company argues that a stable regimen of individually optimized therapy constitutes an adequate implementation of the ACT specified by the G-BA.

The company's justification of its deviation from the ACT is not appropriate. While the company is correct in that the maximum tolerated dose cannot be equated with a drug's approved maximum dose, clear recommendations for treatment escalation based on low-density lipoprotein cholesterol (LDL-C) values exist in the present therapeutic indication. The SPCs for various statins [5-7] define the approved dosage range for children and adolescents and point out that the dosage must be titrated or adjusted based on the individual patient's response and tolerance. The guideline issued by the European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) recommends that the treatment of children with familial hypercholesterolaemia start at a low statin dose and then be escalated until the treatment target (LDL-C < 135 mg/dL) is reached [8]. The S2k Guideline on the Diagnosis and Treatment of Hyperlipidaemia in Children and Adolescents likewise recommends, for paediatric patients, statin uptitration according to individual response and tolerance and based on LDL-C values [9]. Furthermore, the S2k guideline recommends which drugs are to be administered in addition to statin therapy (e.g. ezetimib) if the LDL-C treatment goal is not reached on statin therapy [9]. The guidelines do not, however, recommend a stable treatment regimen irrespective of LDL-C targets. Furthermore, the G-BA's comments on the ACT explicitly state that the continuation of an inadequate therapy (including in terms of its dosage) over the course of a study does not represent an implementation of the ACT unless the maximum tolerated drug therapy has been reached for the individual patient.

All in all, the deviation from the ACT specified by the G-BA has not been adequately justified. The present benefit assessment therefore uses the ACT specified by the G-BA for all research questions.

2.3 Research question 1: Children and adolescents with HeFH aged 10 to 17 years in whom dietary and drug options for lipid lowering have not been exhausted

2.3.1 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 list on evolocumab (status: 4 October 2021)
- bibliographical literature search on evolocumab (last search on 4 October 2021)
- search in trial registries / trial results databases for studies on evolocumab (last search on 4 October 2021)
- search on the G-BA website for evolocumab (last search on 4 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 14 January 2022); for search strategies, see Appendix A of the full dossier assessment

The check of completeness of the study pool did not reveal any relevant RCT for assessing the added benefit of evolocumab in comparison with the ACT. The company, in contrast, used the 24-week HAUSER RCT [10-14].

The HAUSER RCT was unsuitable for deriving any conclusions on the added benefit of evolocumab in comparison with the ACT. Primary reasons for its unsuitability are the following:

- Short study duration of 24 weeks (≥ 12 months minimum study duration for the therapeutic indication of hypercholesterolaemia)
- Wrong population (enrolled patients were not ensured to have received prior therapy with their maximum tolerated statin dose in accordance with evolocumab approval)
- Lack of implementation of the ACT since the study did not allow any adjustments of lipid-lowering therapy to the maximum tolerated drug treatment according to physician's choice over its course even in patients who failed to reach LDL-C targets

Below, the HAUSER RCT is described, and reasoning is provided for its exclusion. Study and intervention characteristics of the HAUSER RCT are presented in Appendix B of the full dossier assessment.

HAUSER RCT presented by the company

The HAUSER RCT is a randomized, controlled, double-blind study comparing evolocumab versus placebo, each in combination with low-fat diet and a stable regimen of lipid-lowering therapy.

It enrolled children and adolescents ≥ 10 and ≤ 17 years who had been diagnosed with HeFH. HeFH was diagnosed on the basis of genetic testing or according to local diagnostic criteria (Simon-Broome Register Group [15], Dutch Lipid Clinic Network [16] or Make Early Diagnosis and Prevent Early Death [MEDPED] [17]). At screening, patients had to exhibit a fasting LDL-C ≥ 130 mg/dL, and they had to have received, for ≥ 4 weeks before LDL-C screening, an approved statin on a stable regimen which the investigator deemed not to require further intensification. Furthermore, patients had to keep a low-fat diet and were allowed to receive additional lipid-lowering drugs, e.g. ezetimib, anion exchange resins, omega-3 fatty acids, or niacin, provided they had been used at a stable dose for ≥ 4 weeks before LDL-C screening or, in case of fibrate treatment, for ≥ 6 weeks before LDL-C screening.

The HAUSER RCT included a total of 158 patients, randomized in a 2:1 ratio to treatment with either evolocumab (N = 105) or placebo (N = 53). Stratification was based on the characteristics of LDL-C at screening (< 160 mg/dL versus ≥ 160 mg/dL) and age at randomization (< 14 years and ≥ 14 years).

Evolocumab treatment was in compliance with the SPC [3] (see Table 10 of the full dossier assessment#2). Furthermore, patients continued the low-fat diet as well as the stable regimen of lipid-lowering therapy as background therapy during study treatment. Adjustments or optimizations of the lipid-lowering therapy were not provided for during the study treatment, except where clinically necessary. However, study documents provide no definition of clinical necessity.

HAUSER-RCT participants were treated for 24 weeks, and after the end of the study, they were allowed to continue or, if they previously received placebo, start evolocumab treatment in the single-arm, open-label HAUSER-OLE extension study (see Table 9 of the full dossier assessment).

The primary outcome of the HAUSER RCT was change in LDL-C value between study start and Week 24. Further outcomes were surveyed in the morbidity and side effects categories.

Unsuitability of the HAUSER RCT presented by the company for the benefit assessment

Insufficient study duration of the HAUSER RCT

In Module 4 A, the company defines a minimum study duration of ≥ 12 weeks as an inclusion criterion, and it included the 24-week HAUSER RCT for assessing the added benefit of evolocumab in comparison with the ACT.

The company's approach is not appropriate because a minimum study duration of 12 months is deemed necessary, as implemented in previous dossier assessments in the therapeutic indication of hypercholesterolaemia [18-23]. Evolocumab 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 evolocumab on patient-relevant outcomes therefore requires a longer follow-up than 12 weeks as defined in the company's inclusion criteria or 24 weeks as used in the HAUSER RCT.

Wrong population (prior therapy with a maximum tolerated dose of a statin not ensured)

As per approval, a precondition for the use of evolocumab in patients eligible for statin therapy is a failure to reach LDL-C targets on the maximum tolerated statin dose [3]. According to German and European guidelines, the recommended LDL-C target for children aged > 10 years is < 135 mg/dL [8,24]. The S2k guideline defines a treatment goal of LDL-C ≤ 130 mg/dL [9].

The HAUSER RCT included patients who, at baseline, already received atorvastatin (N = 68), rosuvastatin (N = 51), pravastatin (N = 19), or simvastatin (N = 18). Most of these patients did not receive a statin dose equal to the maximum dose approved for children with HeFH. For example, only 1 male patient and 1 female patient were treated with the maximum approved dose of atorvastatin (80 mg) [5], while the majority of patients received only 10 mg (N = 20) or 20 mg (N = 31). In accordance with inclusion criteria, the investigator deemed the statin therapy not to require further intensification. However, no reasons are provided as to why intensification of statin therapy would be unnecessary or impossible despite a mean baseline LDL-C value of 184 mg/dL. Also, no criteria were reported on the basis of which investigators ruled out intensification of statin therapy. Patients' baseline statin therapy can therefore not per se be deemed to represent the maximum tolerated dose. The approved maximum dose is not necessarily equal to the maximum tolerated dose (see Section 2.2). In the absence of any provided reasons, however, it is not plausible that only very few patients received the daily maximum dose approved for children and adolescents. The majority of included patients can therefore not be said with certainty to have been treated with the maximum tolerated statin dose and hence to even be indicated for evolocumab treatment.

Appropriate comparator therapy not implemented

For research question 1, the G-BA specified maximum tolerated drug treatment according to physician's choice, taking into account statins, cholesterol absorption inhibitors, and anion exchange resins (see Table 4). As noted by the G-BA, the continuation of an inadequate therapy (including in terms of its dosage) over the course of the study does not represent an implementation of the ACT unless the maximum tolerated drug therapy has been exhausted for a given patient.

Overall, lipid-lowering therapy in the HAUSER RCT comprised 1 statin in almost all participants (except 1 patient in the placebo arm, who received ezetimib monotherapy). Further, a small percentage of the study population additionally received ezetimib (13%), fish oil (4%), phytosterol nos (1%) or colesevelam (1%) as part of their lipid-lowering therapy.

Adjustments of lipid-lowering therapy were not provided for, neither at study start nor over the continued course of the study. Rather, pre-enrolment treatment was to be continued unchanged. While the study protocol allowed adjustments in case of medical necessity, (a) the definition of medical necessity remains unclear and (b) none of the patients received such an adjustment. Hence, the HAUSER RCT did not allow any treatment adjustments for arriving at the maximum tolerated drug therapy, e.g. by combining the existing lipid-lowering therapy with an additional lipid-lowering drug, switching drugs, or dose adjustments. Further, investigators in the HAUSER RCT were blinded, including to lipid parameters, from randomization to 12 weeks after the last treatment with the study drug or the end of the study. 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 according to physician's choice would not even have been possible in the HAUSER RCT.

The failure to implement the maximum tolerated drug therapy is also reflected by the study results on percentage change in LDL-C value: the placebo arm exhibits a nearly unchanged LDL-C value over the course of the study (see Figure 1). Given that the baseline LDL-C values were outside the target range, however, the majority of participants would have been indicated for optimization of lipid-lowering therapy.

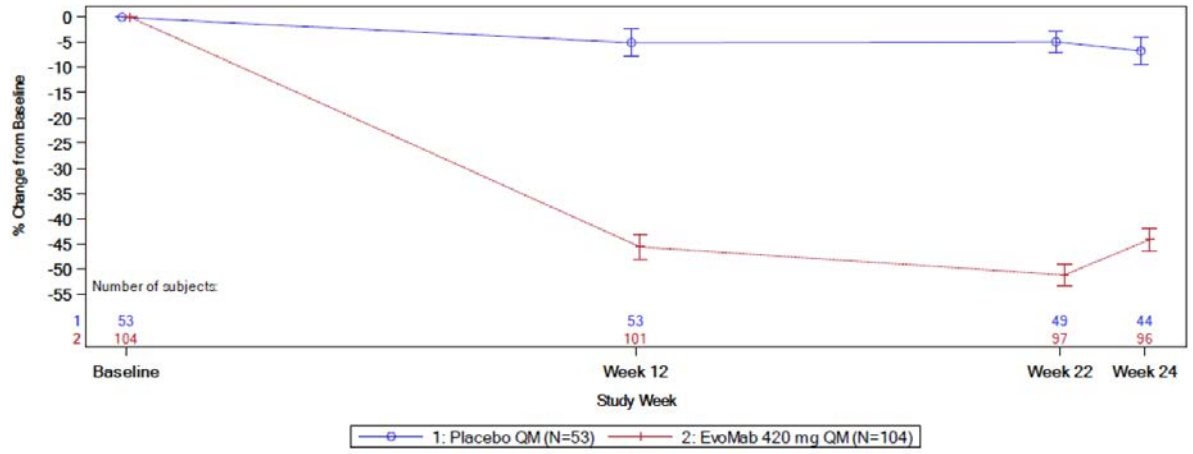

Figure 1: Percent change in LDL-C from baseline to Week 24 of the HAUSER RCT

In summary, the HAUSER RCT compared evolocumab versus placebo. An adequate comparison with maximum tolerated drug treatment according to physician's choice, however, would have required further measures for reducing LDL-C over the course of the study, e.g. dose adjustments or dose escalation, the additional administration of another lipid-lowering drug, or the switch to another lipid-lowering regimen. Overall, the HAUSER RCT therefore failed to implement the ACT specified by the G-BA, maximum tolerated drug therapy according to physician's choice.

2.3.2 Results on added benefit

No suitable data are available for assessing any added benefit of evolocumab in comparison with the ACT in children and adolescents with HeFH aged 10 to 17 years in whom dietary and drug options for lipid lowering have not been exhausted. This results in no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

Since the company did not submit any suitable data for assessing the added benefit of evolocumab in comparison with the ACT in children and adolescents with HeFH aged 10 to 17 years in whom dietary and drug options for lipid lowering have not been exhausted, there is no proof of added benefit of evolocumab in comparison with the ACT for these patients.

This assessment deviates from that by the company, which derived an indication of minor added benefit based on the results of the HAUSER RCT.

2.4 Research question 2: Children and adolescents with HeFH aged 10 to 17 years in whom dietary and drug options for lipid lowering have been exhausted

2.4.1 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 list on evolocumab (status: 4 October 2021)
- bibliographical literature search on evolocumab (last search on 4 October 2021)
- search in trial registries / trial results databases for studies on evolocumab (last search on 4 October 2021)
- search on the G-BA website for evolocumab (last search on 4 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 14 January 2022); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool identified no directly comparative study for this research question.

2.4.2 Results on added benefit

No data are available for assessing any added benefit of evolocumab in comparison with the ACT for children and adolescents with HeFH aged 10 to 17 years in whom dietary and drug options for lipid lowering have been exhausted. This results in no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Since the company did not submit any suitable data for assessing the added benefit of evolocumab in comparison with the ACT in children and adolescents with HeFH aged 10 to 17 years in whom dietary and drug options for lipid lowering have been exhausted, there is no proof of added benefit of evolocumab in comparison with the ACT for these patients.

This concurs with the company's assessment.

2.5 Research question 3: children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have not been exhausted

2.5.1 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 list on evolocumab (status: 4 October 2021)
- bibliographical literature search on evolocumab (last search on 4 October 2021)
- search in trial registries / trial results databases for studies on evolocumab (last search on 4 October 2021)
- search on the G-BA website for evolocumab (last search on 4 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 14 January 2022); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool identified no directly comparative study for the present research question.

In the absence of studies offering a direct comparison, the company conducted an additional information retrieval for further investigations. For the intervention, the company found the single-arm HAUSER-OLE study [25,26]. The company conducted no information retrieval on the ACT.

The single-arm HAUSER-OLE study was unsuitable for deriving any conclusions on the added benefit of evolocumab in comparison with the ACT because it does not allow a comparison with the ACT. The HAUSER-OLE study is described below.

HAUSER-OLE study

The HAUSER-OLE study is a single-arm, open-label extension study with evolocumab. It included 13 patients ≥ 10 to ≤ 17 years with diagnosed HoFH and a fasting LDL-C ≥ 130 mg/dL at screening who were treated with low-fat diet and stable lipid-lowering therapy

(e.g. statins, cholesterol absorption inhibitors, anion exchange resins, niacin, or a combination of these drugs) for ≥ 4 weeks prior to LDL-C screening. Furthermore, the study included 150 patients with HeFH who completed the HAUSER RCT with the allocated investigational drug and without treatment-related serious adverse events (SAEs) (see Table 9 of the full dossier assessment). For the present research question, only the subpopulation aged ≥ 10 and ≤ 11 years with diagnosed HoFH was relevant. This population comprised a total of 6 patients. During the 80-week HAUSER-OLE study, patients were treated with evolocumab as well as background therapy consisting of lipid-lowering therapy and a low-fat diet. Primary outcome of the HAUSER-OLE study was treatment-related adverse events (AEs) by Week 24. Further outcomes were surveyed in the morbidity and side effects categories.

Due to its lack of comparative data, the HAUSER-OLE study was unsuitable for assessing the added benefit of evolocumab in comparison with the ACT. The company likewise did not claim any added benefit for evolocumab, concluding that no added benefit can be derived due to the small case number of only 6 patients and the non-comparative study design.

2.5.2 Results on added benefit

No suitable data are available for assessing any added benefit of evolocumab in comparison with the ACT for children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have not been exhausted. This results in no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

Since the company did not submit any suitable data for assessing the added benefit of evolocumab in comparison with the ACT in children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have not been exhausted, there is no proof of added benefit of evolocumab in comparison with the ACT for these patients.

This concurs with the company's assessment.

2.6 Research question 4: children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have been exhausted

2.6.1 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 list on evolocumab (status: 4 October 2021)
- bibliographical literature search on evolocumab (last search on 4 October 2021)
- search in trial registries / trial results databases for studies on evolocumab (last search on 4 October 2021)

- search on the G-BA website for evolocumab (last search on 4 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 14 January 2022); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool identified no directly comparative study for the present research question. In the absence of studies offering a direct comparison, the company conducted an additional information retrieval for further investigations, but it did not find any relevant studies.

2.6.2 Results on added benefit

No suitable data are available for assessing any added benefit of evolocumab in comparison with the ACT for children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have been exhausted. This results in no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

2.6.3 Probability and extent of added benefit

Since the company did not submit any suitable data for assessing the added benefit of evolocumab in comparison with the ACT in children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have been exhausted, there is no proof of added benefit of evolocumab in comparison with the ACT for these patients.

This concurs with the company’s assessment.

2.7 Probability and extent of added benefit – summary

Table 5 summarizes the result of the assessment of added benefit of evolocumab in comparison with the ACT.

Table 5: Evolocumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Children and adolescents with HeFH[b] aged 10 to 17 years in whom dietary and drug options for lipid lowering have not been exhausted[c]	Maximum tolerated drug treatment according to physician's choice[d], selecting from statins, cholesterol absorption inhibitors, and anion exchange resins	Added benefit not proven
2	Children and adolescents with HeFH[b] aged 10 to 17 years in whom dietary and drug options for lipid lowering have been exhausted[c]	LDL apheresis[e] (as a last resort in refractory disease), if necessary with concomitant lipid-lowering drug treatment	Added benefit not proven
3	Children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have not been exhausted[c]	Maximum tolerated drug treatment according to physician's choice[d], selecting from statins, cholesterol absorption inhibitors, and anion exchange resins	Added benefit not proven
4	Children with HoFH aged 10 to 11 years in whom dietary and drug options for lipid lowering have been exhausted[c]	LDL apheresis[e] (as a last resort in refractory disease), if necessary with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presented is the respective ACT specified by the GBA.
b. In the absence of statin intolerance or contraindication, evolocumab is indicated, according to the approval statement, only for patients with HeFH who do not reach LDL-C targets on the maximum tolerated statin dose [3].
c. According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the German Pharmaceutical Directive [4].
d. As noted by the G-BA, maximum tolerated drug therapy can also comprise a combination of different drug classes; the treatment regimens used in the intervention and comparator arms are assumed to be similar. Furthermore, the continuation of inadequate therapy (including in terms of dosage) over the course of the study does not represent an implementation of the ACT unless the maximum tolerated drug therapy has already been exhausted for the individual patient. A single-comparator study is typically insufficient for implementing treatment according to physician's choice in a directly comparative study.
e. 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; HeFH: heterozygous familial hypercholesterolaemia; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein; LDL-C: LDL cholesterol

The G-BA decides on the added benefit.

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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