IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Assessment module I, Sections I 2.1 to I 2.6, and Assessment module II, Sections II 2.1 to II 2.5, of the dossier assessment *Evolocumab – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 December 2015). Please note: This translation 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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Evolocumab

Assessment module I

Hypercholesterolaemia and mixed dyslipidaemia

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

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Keywords: evolocumab, hypercholesterolemia, benefit assessment

[1] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CHD	coronary heart disease
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDL-C	low-density lipoprotein cholesterol
PAOD	peripheral arterial occlusive disease
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 2 Benefit assessment

I 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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 16 September 2015.

Research question

The aim of the present report was to assess the added benefit of evolocumab as an adjunct to diet and, if applicable, to other lipid-lowering drugs compared with the appropriate comparator therapy (ACT) in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

The G-BA distinguished between different patient groups in its specification of the ACT. Three research questions resulted from this for the assessment; these are presented in Table 1.

Table 1: Research questions and ACTs of the G-BA for the benefit assessment of evolocumab

Research question	Subpopulation	ACT specified by the G-BA[a]
1	Patients for whom statins are an option[b]	Maximum tolerated drug and dietary treatment to reduce lipid levels
2	Patients for whom statin treatment is not an option due to contraindications or treatment-limiting adverse events[b]	Other lipid-lowering drugs (fibrates, anion exchangers, **cholesterol resorption inhibitors**) as monotherapy and dietary lipid-lowering treatment
3	Patients in whom drug and dietary lipid-lowering options have been exhausted, as last resort in refractory disease	LDL apheresis, if applicable together with concomitant lipid-lowering drug treatment

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low-density lipoprotein

According to Appendix III of the Pharmaceutical Directive, patients with existing vascular condition (coronary heart disease [CHD]), cerebrovascular manifestation, peripheral arterial occlusive disease (PAOD)) or at high cardiovascular risk (over 20% event rate/10 years based on the available risk calculators) are exempt from the limitations of prescription of lipid-lowering drugs requiring prescription.

The G-BA specified maximum tolerated drug and dietary treatment to reduce lipid levels as ACT for research question 1. Deviating from the G-BA, the company chose ezetimibe as only

comparator therapy. For research questions 2 and 3, the company followed the G-BA's specification of the ACT and chose the cholesterol resorption inhibitor ezetimibe and dietary treatment to reduce lipid levels as comparator therapy from the options mentioned for research question 2 (patients for whom statins are not an option). The present assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. A minimum study duration of one year was defined for each of the 3 research questions. This deviates from the company's approach, which specified a minimum study duration of 12 weeks.

Results for research question 1: patients for whom statins are an option

For research question 1, the company presented a 12-week randomized, active-controlled study (LAPLACE-2) on the comparison of evolocumab with ezetimibe, each in combination with statins. This study was unsuitable to derive conclusions on the added benefit of evolocumab in patients with primary hypercholesterolaemia or mixed dyslipidaemia for whom statins are an option because it did not fulfil the minimum study duration of one year. Since evolocumab is used in the long-term treatment of a chronic disease, a study duration of at least one year is considered necessary for the assessment of the added benefit.

Hence no relevant data for the assessment of the added benefit of evolocumab in comparison with the ACT were available for research question 1 (patients for whom statins are an option). Hence there was no hint of an added benefit of evolocumab in comparison with the ACT. An added benefit is therefore not proven.

Results for research question 2: patients for whom statins are not an option

For research question 2, the company presented a 12-week randomized, active-controlled study (GAUSS-2) on the comparison of evolocumab with ezetimibe. This study was unsuitable to derive conclusions on the added benefit of evolocumab in patients with primary hypercholesterolaemia or mixed dyslipidaemia for whom statins are not an option because it did not fulfil the minimum study duration of one year. Since evolocumab is used in the long-term treatment of a chronic disease, a study duration of at least one year is considered necessary for the assessment of the added benefit.

Hence no relevant data for the assessment of the added benefit of evolocumab in comparison with the ACT were available for research question 2 (patients for whom statins are not an option). Hence there was no hint of an added benefit of evolocumab in comparison with the ACT. An added benefit is therefore not proven.

Results for research question 3: patients in whom drug and dietary options to reduce lipid levels have been exhausted

The company presented no studies for research question 3 (patients in whom drug and dietary options to reduce lipid levels have been exhausted). Hence there was no hint of an added benefit of evolocumab in comparison with the ACT. An added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[2]

Based on the results presented, the extent and probability of the added benefit of the drug evolocumab in comparison with the ACT for the therapeutic indication of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia is assessed as follows:

An added benefit of evolocumab in comparison with the ACT is not proven for adult patients for whom treatment with statins is an option (research question 1) or for patients for whom such treatment is not an option (research question 2) or for patients in whom drug and dietary options to reduce lipid levels have been exhausted (research question 3).

Table 2 shows a summary of the extent and probability of the added benefit of evolocumab in the therapeutic indication of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

[2] 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, no added benefit, or less benefit). For further details see [1,2].

Table 2: Evolocumab – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Patients for whom statins are an option[b]	Maximum tolerated drug and dietary treatment to reduce lipid levels	Added benefit not proven
Patients for whom statin treatment is not an option due to contraindications or treatment-limiting adverse events[b]	Other lipid-lowering drugs (fibrates, anion exchangers, **cholesterol resorption inhibitors**) as monotherapy and dietary lipid-lowering treatment	Added benefit not proven
Patients in whom drug and dietary lipid-lowering options have been exhausted, as last resort in refractory disease	LDL apheresis, if applicable together with concomitant lipid-lowering drug treatment	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low-density lipoprotein

The G-BA decides on the added benefit.

I 2.2 Research question

The aim of the present report was to assess the added benefit of evolocumab as an adjunct to diet and, if applicable, to other lipid-lowering drugs compared with the ACT in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

The G-BA distinguished between different patient groups in its specification of the ACT. Three research questions resulted from this for the assessment; these are presented in Table 3.

Table 3: Research questions and ACTs of the G-BA for the benefit assessment of evolocumab

Research question	Subpopulation	ACT specified by the G-BA[a]
1	Patients for whom statins are an option[b]	Maximum tolerated drug and dietary treatment to reduce lipid levels
2	Patients for whom statin treatment is not an option due to contraindications or treatment-limiting adverse events[b]	Other lipid-lowering drugs (fibrates, anion exchangers, **cholesterol resorption inhibitors**) as monotherapy and dietary lipid-lowering treatment
3	Patients in whom drug and dietary lipid-lowering options have been exhausted, as last resort in refractory disease	LDL apheresis, if applicable together with concomitant lipid-lowering drug treatment

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive [3].
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low-density lipoprotein

According to Appendix III of the Pharmaceutical Directive, patients with existing vascular condition (CHD, cerebrovascular manifestation, PAOD) or at high cardiovascular risk (over 20% event rate/10 years based on the available risk calculators) are exempt from the limitations of prescription of lipid-lowering drugs requiring prescription [3].

The G-BA specified maximum tolerated drug and dietary treatment to reduce lipid levels as ACT for research question 1. Deviating from the G-BA, the company chose ezetimibe as only comparator therapy (see Section I 2.7.1 of the full dossier assessment). For research questions 2 and 3, the company followed the G-BA's specification of the ACT and chose the cholesterol resorption inhibitor ezetimibe and dietary treatment to reduce lipid levels as comparator therapy from the options mentioned for research question 2 (patients for whom statins are not an option). The present assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. A minimum study duration of one year was defined for each of

the 3 research questions. This deviates from the company's approach, which specified a minimum study duration of 12 weeks.

I 2.3 Research question 1: patients for whom statins are an option

I 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: 25 June 2015)
- bibliographical literature search on evolocumab (last search on 24 June 2015)
- search in trial registries for studies on evolocumab (last search on 30 June 2015)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 1 October 2015)

No relevant study was identified from the check.

Study pool of the company for the direct comparison

From the steps of information retrieval mentioned, the company identified one randomized, active controlled study (LAPLACE-2 [4]) for research question 1. This study was unsuitable to derive conclusions on the added benefit of evolocumab in patients with primary hypercholesterolaemia or mixed dyslipidaemia for whom statins are an option. This is justified below.

In the study LAPLACE-2, evolocumab was compared with ezetimibe, each in combination with dietary treatment and randomly assigned background statin therapy. Primary goal of the study was the investigation of the change in low-density lipoprotein cholesterol (LDL-C) levels in the patients after 12 weeks (the characteristics of the study are presented in I Appendix A, Table 8 and Table 9 of the full dossier assessment).

Due to the short study duration of 12 weeks, the LAPLACE-2 study is unsuitable for the assessment of the added benefit of evolocumab. Evolocumab is designed for use in the long-term treatment of a chronic disease. One main goal of the treatment with lipid-lowering drugs is to reduce risks and complications of vascular diseases. It can be assumed that these outcomes can only be recorded in studies that are conducted over a longer period of time (generally several years). Correspondingly, the Summary of Product Characteristics (SPC) on evolocumab also states that the effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined [5]. Deviating from the company, 12 months were determined as the minimum study duration in the present benefit assessment. The current *Guideline on clinical investigation of medicinal products in the treatment of lipid disorders*

by the European Medicines Agency (EMA) also recommends a study duration of 12 months for drugs with unknown mechanisms of action [6].

Hence no relevant data for the assessment of the added benefit of evolocumab in comparison with the ACT were available for research question 1.

I 2.3.2 Results on added benefit

In its dossier, the company presented no relevant data for the assessment of the added benefit of evolocumab in patients with primary hypercholesterolaemia or mixed dyslipidaemia for whom statin treatment is an option. Hence there was no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

I 2.3.3 Extent and probability of added benefit

Since the company presented no suitable data for patients with primary hypercholesterolaemia or mixed dyslipidaemia for whom statin treatment is an option, an added benefit of evolocumab for these patients is not proven.

I 2.3.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

I 2.4 Research question 2: patients for whom statins are not an option

I 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: 25 June 2015)
- bibliographical literature search on evolocumab (last search on 24 June 2015)
- search in trial registries for studies on evolocumab (last search on 30 June 2015)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 1 October 2015)

No relevant study was identified from the check.

Study pool of the company for the direct comparison

From the steps of information retrieval mentioned, the company identified one randomized, active controlled study (GAUSS-2 [7]) for research question 2. This study was unsuitable to derive conclusions on the added benefit of evolocumab in patients with primary hypercholesterolaemia or mixed dyslipidaemia for whom statins are not an option. This is justified below.

Evolocumab was compared with ezetimibe in the GAUSS-2 study. Patients who had not tolerated at least 2 previous statin treatments were included in the study. Primary goal of this study was the investigation of the change in LDL-C levels in the patients after 12 weeks (the characteristics of the study are presented in I Appendix A, Table 10 and Table 11 of the full dossier assessment).

The study duration of the GAUSS-2 study was 12 weeks; therefore the justification for its exclusion mentioned in Section I 2.3.1 also applies to this study. Due to the short study duration, the GAUSS-2 study is unsuitable for the assessment of the added benefit of evolocumab.

Hence no relevant data for the assessment of the added benefit of evolocumab in comparison with the ACT were available for research question 2.

I 2.4.2 Results on added benefit

In its dossier, the company presented no relevant data for the assessment of the added benefit of evolocumab in patients with primary hypercholesterolaemia or mixed dyslipidaemia for whom statin treatment is not an option. Hence there was no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

I 2.4.3 Extent and probability of added benefit

Since the company presented no suitable data for patients with primary hypercholesterolaemia or mixed dyslipidaemia for whom statin treatment is not an option, an added benefit of evolocumab for these patients is not proven.

I 2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

I 2.5 Research question 3: patients in whom drug and dietary options to reduce lipid levels have been exhausted

I 2.5.1 Information retrieval and study pool

The information retrieval on research questions 1 and 2 was the source of the company's information retrieval on research question 3.

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: 25 June 2015)
- bibliographical literature search on evolocumab (last search on 24 June 2015)
- search in trial registries for studies on evolocumab (last search on 30 June 2015)

- bibliographical literature search on the ACT (the dossier contained no information on the search date)
- search in trial registries for studies on the ACT (last search on 13 July 2015)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 1 October 2015)

The company identified no relevant studies. No relevant study was identified from the check either.

I 2.5.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of evolocumab in patients with primary hypercholesterolaemia or mixed dyslipidaemia in whom drug and dietary lipid-lowering options have been exhausted. Hence there was no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

I 2.5.3 Extent and probability of added benefit

Since the company presented no data for patients with primary hypercholesterolaemia or mixed dyslipidaemia in whom drug and dietary lipid-lowering options have been exhausted, an added benefit of evolocumab for these patients is not proven.

I 2.5.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

I 2.6 Extent and probability of added benefit – summary

Table 4 summarizes the result of the assessment of the added benefit of evolocumab in comparison with the ACT in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

Table 4: Evolocumab – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Patients for whom statins are an option[b]	Maximum tolerated drug and dietary treatment to reduce lipid levels	Added benefit not proven
Patients for whom statin treatment is not an option due to contraindications or treatment-limiting adverse events[b]	Other lipid-lowering drugs (fibrates, anion exchangers, **cholesterol resorption inhibitors**) as monotherapy and dietary lipid-lowering treatment	Added benefit not proven
Patients in whom drug and dietary lipid-lowering options have been exhausted, as last resort in refractory disease	LDL apheresis, if applicable together with concomitant lipid-lowering drug treatment	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive [3].
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low-density lipoprotein

In summary, an added benefit of evolocumab in comparison with the ACT in the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia is not proven for adult patients for whom treatment with statins is an option or for patients for whom such treatment is not an option or for patients in whom drug and dietary options to reduce lipid levels have been exhausted.

The overall assessment deviates from that of the company, which derived an indication of a non-quantifiable added benefit both for patients for whom statins are an options and for patients for whom statins are not an option.

The G-BA decides on the added benefit.

References for English extract

Please see full assessment for full reference list.

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Evolocumab

Assessment module II

Homozygous familial hypercholesterolaemia

Medical and scientific advice:

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

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- Michaela Florina Kerekes
- Anja Schwalm
- Ulrike Seay
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Keywords: evolocumab, hypercholesterolemia, benefit assessment

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List of abbreviations

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

II 2 Benefit assessment

II 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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 16 September 2015.

Research question

The aim of the present report was to assess the added benefit of evolocumab in combination with other lipid-lowering treatments in comparison with the appropriate comparator therapy (ACT) in adult and adolescent patients 12 years and older with homozygous familial hypercholesterolaemia (HoFH).

The G-BA distinguished between different patient groups in the specification of the ACT. This resulted in 2 research questions for the assessment. Research question 2 was subdivided into patients who have not yet received LDL apheresis (2A) and patients who have already received LDL apheresis (2B).

Table 1 shows the research questions relevant for the present benefit assessment and the respective ACTs.

Table 1: Research questions and ACTs of the G-BA for the benefit assessment of evolocumab

Research question	Subpopulation	Experimental intervention	ACT specified by the G-BA
1	Patients in whom drug and dietary lipid-lowering options have not been exhausted	Evolocumab	Maximum tolerated drug and dietary treatment to reduce lipid levels
2A	Patients in whom drug and dietary lipid-lowering options have been exhausted and who do not receive LDL apheresis treatment	Evolocumab	LDL apheresis (as "last resort" in refractory disease), if necessary with concomitant lipid-lowering drug treatment
2B	Patients in whom drug and dietary lipid-lowering options have been exhausted and who receive concomitant LDL apheresis treatment	Evolocumab as add-on therapy to LDL apheresis	
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low-density lipoprotein			

The company generally followed the G-BA's specification, but in research question 2 did not differentiate between patients who receive no LDL apheresis (2A) and patients who receive LDL apheresis (2B).

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. A minimum study duration of one year was defined for each research question. This deviates from the company's approach, which specified a minimum study duration of 12 weeks.

Results for research question 1: patients in whom drug and dietary lipid-lowering options have not been exhausted

For research question 1, the company presented a 12-week randomized controlled trial (RCT) (TESLA) on the comparison of evolocumab with placebo, each in combination with ongoing lipid-lowering drug treatment. This study was unsuitable to derive conclusions on the added benefit of evolocumab in patients with HoFH in whom drug and dietary lipid-lowering options have not been exhausted because it did not fulfil the minimum study duration of one year. Since evolocumab is used in the long-term treatment of a chronic disease, a study duration of at least one year is considered necessary for the assessment of the added benefit.

Hence no relevant data for the assessment of the added benefit of evolocumab in comparison with the ACT were available for research question 1 (patients for whom drug and dietary lipid-lowering options have not been exhausted). Hence there was no hint of an added benefit of evolocumab in comparison with the ACT. An added benefit is therefore not proven.

Results for research question 2: patients in whom drug and dietary lipid-lowering options have been exhausted

The company presented no studies for research question 2 (patients in whom drug and dietary lipid-lowering options have been exhausted). Hence there was no hint of an added benefit of evolocumab in comparison with the ACT. An added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit

On the basis of the results presented, the extent and probability of the added benefit of the drug evolocumab compared with the ACT for the therapeutic indication of HoFH is assessed as follows:

An added benefit of evolocumab in comparison with the ACT in the treatment of adult and adolescent patients 12 years and older is not proven for patients in whom drug and dietary lipid-lowering options have not been exhausted (research question 1) or for patients in whom drug and dietary lipid-lowering options have been exhausted (research question 2).

Table 2 presents a summary of the extent and probability of the added benefit of evolocumab in the therapeutic indication of HoFH.

Table 2: Evolocumab – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Patients in whom drug and dietary lipid-lowering options have not been exhausted	Maximum tolerated drug and dietary treatment to reduce lipid levels	Added benefit not proven
Patients in whom drug and dietary lipid-lowering options have been exhausted and who do not receive LDL apheresis treatment	LDL apheresis (as "last resort" in refractory disease), if necessary with concomitant lipid-lowering drug treatment	Added benefit not proven
Patients in whom drug and dietary lipid-lowering options have been exhausted and who do receive concomitant LDL apheresis treatment		Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low-density lipoprotein		

The G-BA decides on the added benefit.

II 2.2 Research question

The aim of the present report was to assess the added benefit of evolocumab in combination with other lipid-lowering treatments in comparison with the ACT in adult and adolescent patients 12 years and older with HoFH.

The G-BA distinguished between different patient groups in the specification of the ACT. This resulted in 2 research questions for the assessment. Research question 2 was subdivided into patients who have not yet received LDL apheresis (2A) and patients who have already received LDL apheresis (2B).

Table 3 shows the research questions relevant for the present benefit assessment and the respective ACTs.

Table 3: Research questions and ACTs of the G-BA for the benefit assessment of evolocumab

Research question	Subpopulation	Experimental intervention	ACT specified by the G-BA
1	Patients in whom drug and dietary lipid-lowering options have not been exhausted	Evolocumab	Maximum tolerated drug and dietary treatment to reduce lipid levels
2A	Patients in whom drug and dietary lipid-lowering options have been exhausted and who do not receive LDL apheresis treatment	Evolocumab	LDL apheresis (as “last resort” in refractory disease), if necessary with concomitant lipid-lowering drug treatment
2B	Patients in whom drug and dietary lipid-lowering options have been exhausted and who receive concomitant LDL apheresis treatment	Evolocumab as add-on therapy to LDL apheresis	
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low-density lipoprotein			

The company generally followed the G-BA’s specification, but in research question 2 did not differentiate between patients who receive no LDL apheresis (2A) and patients who receive LDL apheresis (2B).

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. A minimum study duration of one year was defined for each research question. This deviates from the company’s approach, which specified a minimum study duration of 12 weeks.

II 2.3 Research question 1: patients in whom drug and dietary lipid-lowering options have not been exhausted

II 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: 25 June 2015)
- bibliographical literature search on evolocumab (last search on 24 June 2015)
- search in trial registries for studies on evolocumab (last search on 30 June 2015)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 1 October 2015)

No relevant study was identified from the check.

Study pool of the company for the direct comparison

From the steps of information retrieval mentioned, the company identified one RCT (TESLA [1]) for research question 1. This study was unsuitable to derive conclusions on the added benefit of evolocumab in patients with HoFH in whom drug and dietary lipid-lowering options have not been exhausted. This is justified below.

In the TESLA study, evolocumab was compared with placebo in HoFH patients. Patients in both study arms continued their ongoing dietary and drug lipid-lowering treatment. Primary goal of this study was the investigation of the change in low-density lipoprotein cholesterol (LDL-C) levels after 12 weeks (the characteristics of the study are presented in II Appendix A, Table 8 and Table 9 of the full dossier assessment).

Due to the short study duration of 12 weeks, the TESLA study was unsuitable for the assessment of the added benefit of evolocumab. Evolocumab is designed for use in the long-term treatment of a chronic disease. One main goal of the treatment with lipid-lowering drugs is to reduce risks and complications of vascular diseases. It can be assumed that these outcomes can only be recorded in studies that are conducted over a longer period of time (generally several years). Correspondingly, the Summary of Product Characteristics (SPC) on evolocumab also states that the effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined [2]. Deviating from the company, 12 months were determined as the minimum study duration in the present benefit assessment. The current *Guideline on clinical investigation of medicinal products in the treatment of lipid disorders* by the European Medicines Agency (EMA) also recommends a study duration of 12 months for drugs with unknown mechanisms of action [3].

Moreover, the implementation of the ACT in the TESLA study was questionable. The present research questions comprises patients whose drug and dietary lipid-lowering options have not been exhausted**.** The corresponding ACT was the maximum tolerated drug and dietary lipid-lowering treatment. HoFH patients on stable lipid-lowering drug treatment who received no apheresis were included in the TESLA study. There was no information about whether the patients' drug treatments already were the maximum exhausted treatment. In addition to their ongoing treatment, the patients received evolocumab or placebo in the study according to randomization. No dose adjustments of the lipid-lowering basic therapy were envisaged in

both study arms. The patients' drug treatments were not allowed to be exhausted before the study in order to concur with the present research question. The study should have had the option to adjust the patients' lipid-lowering basic treatments to concur with the ACT maximum tolerated lipid-lowering treatment. If, in contrast, the options of lipid-lowering treatments had been exhausted in the patients already before the start of the study (research question 2A), the ACT in the comparator group would have been LDL apheresis.

Hence no relevant data for the assessment of the added benefit of evolocumab in comparison with the ACT were available for research question 1.

II 2.3.2 Results on added benefit

In its dossier, the company presented no relevant data for the assessment of the added benefit of evolocumab in patients with HoFH in whom drug and dietary lipid-lowering options have not been exhausted. Hence there was no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

II 2.3.3 Extent and probability of added benefit

Since the company presented no suitable data for patients with HoFH in whom drug and dietary lipid-lowering options have not been exhausted, an added benefit of evolocumab for these patients is not proven.

II 2.3.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

II 2.4 Research question 2A and 2B: patients in whom drug and dietary lipid-lowering options have been exhausted

II 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: 25 June 2015)
- bibliographical literature search on evolocumab (last search on 24 June 2015)
- search in trial registries for studies on evolocumab (last search on 30 June 2015)
- bibliographical literature search on the ACT (9 July 2015)
- search in trial registries for studies on the ACT (last search on 13 July 2015)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 1 October 2015)

The company did not identify any relevant studies. No relevant study was identified from the check either.

II 2.4.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of evolocumab in patients with HoFH in whom drug and dietary lipid-lowering options have been exhausted. Hence there was no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

II 2.4.3 Extent and probability of added benefit

Since the company presented no suitable data for patients with HoFH in whom drug and dietary lipid-lowering options have been exhausted, an added benefit of evolocumab for these patients is not proven.

II 2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

II 2.5 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of evolocumab in comparison with the ACT in patients with HoFH is summarized in Table 4.

Table 4: Evolocumab – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Patients in whom drug and dietary lipid-lowering options have not been exhausted	Maximum tolerated drug and dietary treatment to reduce lipid levels	Added benefit not proven
Patients in whom drug and dietary lipid-lowering options have been exhausted and who do not receive LDL apheresis treatment	LDL apheresis (as “last resort” in refractory disease), if necessary with concomitant lipid-lowering drug treatment	Added benefit not proven
Patients in whom drug and dietary lipid-lowering options have been exhausted and who do receive concomitant LDL apheresis treatment		Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low-density lipoprotein		

In summary, an added benefit of evolocumab in comparison with the ACT in the treatment of HoFH in adult and adolescent patients 12 years and older is not proven for patients in whom drug and dietary lipid-lowering options have not been exhausted (research question 1) or for

patients in whom drug and dietary lipid-lowering options have been exhausted (research question 2).

The overall assessment deviates from that of the company, which derived an indication of a non-quantifiable added benefit for the total target population.

The G-BA decides on the added benefit.

References for English extract

Please see full assessment for full reference list.

1. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet 2015; 85(9965): 341-350.

2. Amgen. Repatha 140 mg Injektionslösung in einem Fertigpen: Fachinformation [online]. July 2015 [accessed: 12 November 2015]. URL: http://www.fachinfo.de.

3. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of lipid disorders [online]. 19 December 2013 [accessed: 27 October 2015]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/01/WC500159540.pdf.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-38-evolocumab-nutzenbewertung-gemaess-35a-sgb-v.6942.html.