IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Evolocumab (heterozygous hypercholesterolaemia and mixed dyslipidaemia) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of Sections 2.1 to 2.6 and of Appendix A of the dossier assessment *Evolocumab (heterozygote Hypercholesterinämie und gemischte Dyslipidämie) – Nutzenbewertung gemäß § 35a SGB V (neue wissenschaftliche Erkenntnisse)* (Version 1.0; Status: 12 June 2018). 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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[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)
HDL-C	high-density lipoprotein cholesterol
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)

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 pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier on the drug to be evaluated on 16 September 2015 for the early benefit assessment. The company now requested a new benefit assessment for a subindication – primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia – because of new scientific findings. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 15 March 2018.

Research question

The aim of the present report was to assess the added benefit of evolocumab as an adjunct to diet and possibly 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.

Evolocumab is also approved for the treatment of homozygous familial hypercholesterolaemia. This subindication is not subject of the present assessment.

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 2.

Table 2: Research questions of the benefit assessment of evolocumab

Research question	Subindication	ACT[a]
1	Patients who are eligible for statin therapy[b]	Maximum tolerated drug and dietary treatment to reduce lipid levels
2	Patients who are not eligible for statin therapy due to statin intolerance or contraindications	Lipid-lowering drugs other than statins (fibrates, anion exchangers, cholesterol resorption inhibitors) as monotherapy and dietary lipid-lowering therapy
3	Patients in whom drug and dietary options to reduce lipid levels have been exhausted	LDL apheresis (as "last resort" in refractory disease)[c], possibly with concomitant lipid-lowering drug treatment

a: Presentation of the respective ACT specified by the G-BA.
b: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive. Not reaching LDL-C goals with the maximum tolerated dose of a statin is an additional precondition for an approval-compliant use of evolocumab.
c: It is a general precondition that LDL-C cannot be lowered sufficiently with documented maximum dietary and drug treatment for at least 12 months.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low density lipoprotein; LDL-C: LDL cholesterol

According to the approval, not reaching low-density lipoprotein cholesterol (LDL-C) goals with the maximum tolerated dose of a statin is a precondition for the use of evolocumab for patients who are eligible for statin therapy (research question 1).

The company cited maximum tolerated drug and dietary treatment to reduce lipid levels as ACT for research question 1. According to further information in the dossier, however, it restricted the drug treatment to reduce lipid levels to ezetimibe as primary treatment option. This restriction is not meaningful with regard to content and does not concur with the G-BA's specification. It was therefore not followed. For research question 3, the company followed the G-BA's specification in the choice of the ACT. Research question 2 was not part of the company's dossier. The company justified this with the lack of data that would be considered in a benefit assessment procedure.

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 1 year were used for the derivation of the added benefit. Against the background of long-term treatment, a longer study duration was considered adequate also for research question 3, for which the company specified a minimum study duration of 4 weeks, to allow the assessment of the long-term effects of evolocumab and a reduction in the frequency of LDL-C apheresis on patient-relevant outcomes.

Results

Research question 1: patients who are eligible for statin therapy

For research question 1, the company presented a double-blind, multicentre RCT (FOURIER) on the comparison of evolocumab versus placebo, each in combination with stable lipid-lowering background therapy.

This study was unsuitable to derive conclusions on the added benefit of evolocumab in patients with primary hypercholesterolaemia or mixed dyslipidaemia who are eligible for statin therapy.

- On the one hand, it was not ensured that patients received prior therapy with a maximum tolerated dose of a statin, which is a precondition for an approval-compliant use of evolocumab.
- On the other, the comparator in the study did not concur with the G-BA's ACT of a maximum tolerated drug and dietary treatment to reduce lipid levels. Concurring with the research question (patients unable to reach LDL-C goals with the maximum tolerated dose of a statin), an escalation of the ongoing lipid-lowering therapy is required for an adequate implementation of the ACT. There was no such treatment escalation in the comparator arm of the FOURIER study.

Hence, no relevant data for the assessment of the added benefit of evolocumab in comparison with the ACT were available for research question 1. This resulted in no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: patients who are not eligible for statin therapy due to statin intolerance or contraindications

Research question 2 was not part of the company's dossier. Hence, no data were available for a benefit assessment. For research question 2, this resulted in no hint of an added benefit of evolocumab in comparison with the ACT; an added benefit is therefore not proven.

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

For research question 3, the company presented a 6-week randomized, active-controlled study (APHERESE) on the comparison of evolocumab versus LDL apheresis, each in combination with a lipid-lowering pharmacological background therapy. Due to the short duration of its randomized study phase of only 6 weeks, this study was unsuitable to derive conclusions on the added benefit of evolocumab in patients with primary hypercholesterolaemia or mixed dyslipidaemia in whom drug and dietary options to reduce lipid levels have been exhausted. Against the background of long-term treatment, a longer study duration was considered adequate also for this patient population, to allow the assessment of the long-term effects of evolocumab and a reduction in the frequency of LDL-C apheresis on patient-relevant outcomes.

Hence, no relevant data for the assessment of the added benefit of evolocumab in comparison with the ACT were available for research question 3. This resulted 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 the added benefit of the drug evolocumab in comparison with the ACT are assessed as follows:

An added benefit of evolocumab in comparison with the ACT is not proven for any of the 3 research questions.

Table 3 presents a summary of the probability and extent of the 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

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Patients who are eligible for statin therapy[b]	Maximum tolerated drug and dietary treatment to reduce lipid levels	Added benefit not proven
Patients who are not eligible for statin therapy due to statin intolerance or contraindications	Lipid-lowering drugs other than statins (fibrates, anion exchangers, cholesterol resorption inhibitors) as monotherapy and dietary lipid-lowering therapy	Added benefit not proven
Patients in whom drug and dietary options to reduce lipid levels have been exhausted	LDL apheresis (as "last resort" in refractory disease)[c] possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive. Not reaching LDL-C goals with the maximum tolerated dose of a statin is an additional precondition for an approval-compliant use of evolocumab.
c: It is a general precondition that LDL-C cannot be lowered sufficiently with documented maximum dietary and drug treatment for at least 12 months.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low density lipoprotein; LDL-C: LDL cholesterol

The G-BA decides on the added benefit.

2.2 Research question

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

Evolocumab is also approved for the treatment of homozygous familial hypercholesterolaemia. This subindication is not subject of the present assessment.

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 4.

Table 4: Research questions of the benefit assessment of evolocumab

Research question	Subindication	ACT[a]
1	Patients who are eligible for statin therapy[b]	Maximum tolerated drug and dietary treatment to reduce lipid levels
2	Patients who are not eligible for statin therapy due to statin intolerance or contraindications	Lipid-lowering drugs other than statins (fibrates, anion exchangers, cholesterol resorption inhibitors) as monotherapy and dietary lipid-lowering therapy
3	Patients in whom drug and dietary options to reduce lipid levels have been exhausted	LDL apheresis (as "last resort" in refractory disease)[c], possibly with concomitant lipid-lowering drug treatment

a: Presentation of the respective ACT specified by the G-BA.
b: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive [4]. Not reaching LDL-C goals with the maximum tolerated dose of a statin is an additional precondition for an approval-compliant use of evolocumab [5].
c: It is a general precondition that LDL-C cannot be lowered sufficiently with documented maximum dietary and drug treatment for at least 12 months [6].
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low density lipoprotein; LDL-C: LDL cholesterol

According to the approval, not reaching LDL-C goals with the maximum tolerated dose of a statin is a precondition for the use of evolocumab for patients who are eligible for statin therapy (research question 1) [5].

The company cited maximum tolerated drug and dietary treatment to reduce lipid levels as ACT for research question 1. According to further information in the dossier, however, it restricted the drug treatment to reduce lipid levels to ezetimibe as primary treatment option. This restriction is not meaningful with regard to content and does not concur with the G-BA's specification. It was therefore not followed. For research question 3, the company followed the G-BA's specification in the choice of the ACT. Research question 2 was not part of the company's dossier. The company justified this with the lack of data that would be considered in a benefit assessment procedure.

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 1 year were used for the derivation of the added benefit. Against the background of long-term treatment, a longer study duration was considered adequate also for research question 3, for which the company specified a minimum study duration of 4 weeks, to allow the assessment of the long-term effects of evolocumab and a reduction in the frequency of LDL-C apheresis on patient-relevant outcomes.

2.3 Research question 1: patients who are eligible for statin therapy

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: 1 March 2018)
- bibliographical literature search on evolocumab (last search on 1 March 2018)
- search in trial registries for studies on evolocumab (last search on 1 March 2018)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 21 March 2018)

No relevant study was identified from the check.

Study pool of the company

From the steps of information retrieval mentioned for research question 1, the company identified one RCT (FOURIER [7-10]). The FOURIER study was unsuitable to derive conclusions on the added benefit of evolocumab versus the ACT in patients with primary hypercholesterolaemia or mixed dyslipidaemia who are eligible for statin therapy. The following reasons in particular were decisive for this:

- wrong population (it was not ensured that patients received prior therapy with a maximum tolerated dose of a statin)
- wrong comparator therapy (the comparator did not concur with the ACT specified by the G-BA)

This is justified in detail below.

Description of the FOURIER study

The FOURIER study was a double-blind, multicentre RCT. It included adult patients with a history of clinically evident cardiovascular disease and at least 1 additional major or at least 2 additional other risk factors.

An initial screening was followed by a pretreatment phase of at most 15 weeks, during which all patients were to be adjusted to lipid-lowering therapies individually optimized according to the clinical practice guidelines (CPGs) of local professional societies. After a stable lipid-lowering therapy of 4 weeks and LDL-C values of ≥ 70 mg/dL or non-high-density lipoprotein cholesterol (non-HDL-C) values of ≥ 100 mg/dL, the patients were randomized to the treatment arms. A total of 27 654 patients were randomly allocated in a 1:1 ratio to treatment with evolocumab or placebo, each in combination with the stable lipid-lowering background therapy.

Primary outcome of the study was a composite outcome, defined as the time to first event of 1 of the following 5 events: cardiovascular death (including fatal myocardial infarction and fatal stroke), nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina pectoris or coronary revascularization. Secondary "key outcome" was also a composite outcome, defined as time to first event of 1 of the following 3 events: cardiovascular death (including fatal myocardial infarction and fatal stroke), nonfatal myocardial infarction or nonfatal stroke. Besides cardiovascular events, changes in lipid levels and side effects were also recorded. The characteristics of the study are presented in Appendix A.1.

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

According to the approval, not reaching LDL-C goals with the maximum tolerated dose of a statin is a precondition for the use of evolocumab in patients who are eligible for statin therapy [5].

In the FOURIER study, the physician was to optimize the lipid-lowering therapy for the individual patients during the screening phase (i.e. before randomization). A daily statin dose of 20 mg atorvastatin or equivalent[4] was a precondition for the inclusion in the randomized phase of the FOURIER study; a daily statin dose of at least 40 mg atorvastatin or equivalent[1] was recommended. The physician had to provide reasons if patients were not receiving the recommended dose of at least 40 mg atorvastatin (but only if their LDL-C level was > 100 mg/dL [see also Appendix A.1, Table 10]). According to the case report form (CRF), a possible reason was that the patient's individual lipid goal had been reached, for example.

The following 2 problems result from these inclusion criteria regarding the preconditions for use of evolocumab mentioned above:

1) The statin dose of at least 40 mg atorvastatin or equivalent daily recommended in the study cannot be considered per se to be the maximum tolerated dosage because the approved maximum daily dose according to the Summary of Product Characteristics (SPC) without restrictions is 80 mg for atorvastatin and 20 mg for rosuvastatin [11,12]. This is twice the dose for each of the doses recommended in the study. It can be inferred from the study documents that only a proportion of 29% of all included patients received the maximum statin dose of 80 mg atorvastatin or equivalent and therefore demonstrably concurred with the research question (see also Appendix A.1, Table 12). Another 5% of the patients received statins in combination with ezetimibe; information on the dose of the statin was not provided. Even under the assumption that these patients already received a maximum tolerated dose of a statin according to the preconditions for the use of ezetimibe, this would only amount to a total of about 1 third (34%) of the study population of the research question. The vast majority of the patients did not receive the

[4] 20 mg atorvastatin equivalent correspond to 40 mg simvastatin, 5 mg rosuvastatin or 4 mg pitavastatin; at least 40 mg atorvastatin equivalent correspond to 80 mg simvastatin or at least 10 mg rosuvastatin

maximum statin dose (about 39% received a statin dose of 40 mg atorvastatin or equivalent; about 26% received a statin dose of 20 mg atorvastatin or equivalent). A justification for the non-maximum dosage was only required in the framework of the study if 20 mg atorvastatin or equivalent were administered; the company did not provide such a justification. It can therefore not be assumed that the patients with 20 or 40 mg atorvastatin or equivalent were receiving their maximum tolerated dose of a statin.

2) All patients for whom the physician justified a low statin dose with the fact that their individual lipid goals had been reached are not approved for treatment with evolocumab and hence do not concur with the research question in any case. The company presented no data on the proportion of these patients in the study.

Overall, only fewer than 1 third of the patients included in the FOURIER study demonstrably complied with the present research question. It was not shown for a large proportion of the patients included in the FOURIER study that they received a maximum tolerated dose of a statin. On the contrary, the design of the FOURIER study explicitly mandated that a submaximum statin dose could be sufficient if individual treatment goals were reached. The company presented no subgroup analyses for patients who demonstrably received a maximum tolerated lipid-lowering therapy.

Wrong comparator therapy (G-BA specification not implemented)

The G-BA specified maximum tolerated drug and dietary treatment to reduce lipid levels as ACT for research question 1. Concurring with the research question (patients unable to reach LDL-C goals with the maximum tolerated dose of a statin), an escalation of the ongoing lipid-lowering therapy is required for an adequate implementation of the ACT. There was no such treatment escalation in the comparator arm of the FOURIER study.

In the FOURIER study, lipid-lowering therapy was to be optimized for the individual patients before randomization. After randomization, the patients received either evolocumab or placebo in addition to this stable background therapy. As described in the previous section, only about 29% of the patients were receiving the maximum statin dose at the time point of randomization; it was not ensured for the remaining study population that patients were receiving their maximum tolerated dose of a statin in each case. Only few patients were receiving further lipid-lowering therapies besides statins at the time point of randomization: Only 5% were receiving a combination therapy of a statin and ezetimibe, about 3% were receiving fibrates, 0.5% nicotinic acid derivatives, and 0.1% anion exchangers (see Appendix A.1, Table 12).

The lipid-lowering background therapy was to be continued without changes in both treatment arms during the entire study and was only allowed to be adapted in exceptional cases and after consultation with the company. The fact that therefore no treatment escalation was possible in the placebo arm was also reflected in the study results: Only a fraction of the patients received further escalation of their lipid-lowering therapies in the course of the study. According to the study documents, only 1.0% of the patients in the placebo arm received an up-titration of their

statin doses. Statins other than atorvastatin, simvastatin, rosuvastatin or pitavastatin were not allowed. Only 1.1% of the patients in the placebo arm initiated treatment with ezetimibe [13]. The study results on the course of the LDL-C values after randomization presented in Figure 1 also confirm that no further drug interventions to lower lipid levels were delivered in the placebo arm in the course of the study.

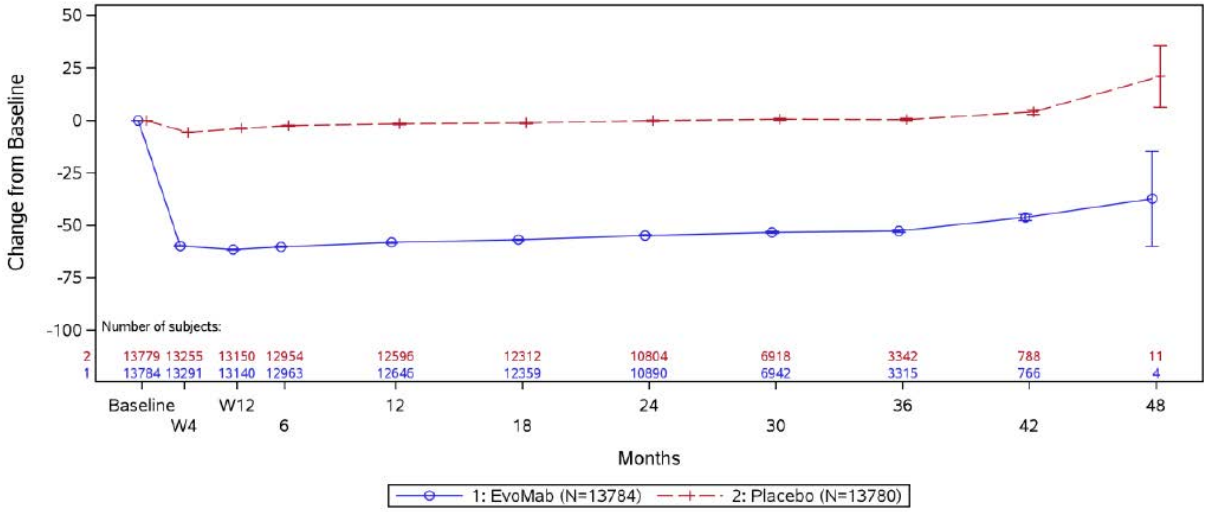

Figure 1: Mean change of the LDL-C level in mg/dL in dependence on study visit and treatment in the FOURIER study

Hence, the study ultimately compared evolocumab versus placebo. For an adequate comparison with a maximum tolerated drug and dietary treatment, it would have been necessary to further optimize the lipid-lowering background therapy for the individual patient in the placebo group, for example by adjusting the dose, by adding another lipid-lowering drug, or by switching to a different lipid-lowering therapy.

Overall, treatment in the control arm of the FOURIER study did therefore not concur with the G-BA's ACT of a maximum tolerated drug and dietary treatment to reduce lipid levels. Hence, the study would not be suitable for the assessment of the added benefit of evolocumab in comparison with the ACT even if it was possible to delineate a subpopulation that was previously treated with maximum tolerated statin therapy (see above).

Irrespective of this, the company's approach to use the FOURIER study as relevant for research question 1 contradicts its own approach in the dossier on the first assessment of evolocumab [14]. The comparison of evolocumab with placebo as add-on to a stable lipid-lowering background therapy in the FOURIER study concurs with the treatment in the control arm of the DESCARTES study [15]. In the first dossier on the benefit assessment of evolocumab, the company did not use this study to prove the added benefit with the justification that it was a placebo-controlled study. The G-BA's decision also found that the ACT was not implemented in this study [16].

Supplementary consideration of the results of the FOURIER study

Irrespective of the missing relevance of the results of the FOURIER study for the present benefit assessment, these results are presented in Appendix A.2 as additional information.

Primary and secondary composite outcomes in the FOURIER study

In Module 4 A, the company presented the results of the primary composite outcome (defined as time to cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina pectoris or coronary revascularization) and of the secondary composite outcome (defined as time to cardiovascular death, myocardial infarction or stroke). The primary composite outcome of the study comprised components of different clinical importance – mortality due to myocardial infarction or stroke is of different importance and constitutes different severity for patients than hospitalization, for example. In addition, it was not comprehensible for the components on coronary revascularizations to what extent these were urgent. For this reason, Appendix A.2 only presents results on the secondary composite outcome and its individual components as well as further patient-relevant outcomes.

Results of the FOURIER study

The results of the FOURIER study showed a statistically significant difference in the secondary composite outcome for the total population (fewer events under evolocumab). This difference was mainly caused by the individual components "nonfatal myocardial infarction" and "nonfatal stroke", whereas no statistically significant difference was shown for cardiovascular mortality. A relevant effect modification by the subgroup characteristic "geographical region" was shown for this composite outcome. This is described in more detail in the following section.

No statistically significant differences between the treatment groups were shown for all-cause mortality and side effects. There were no results on health-related quality of life.

Relevant effect modification by the subgroup characteristic "geographical region"

The multicentre FOURIER study was conducted in a total of 1242 centres in Europe, North America, Latin America and in the Asian-Pacific region. Heterogeneous quality of health care can therefore be assumed. This particularly applies to the individual optimization of the lipid-lowering therapy in the screening phase, which was to be conducted under consideration of the CPGs of local professional societies. There was no information on this, e.g. regarding lipid-lowering background therapy by region.

Geographical region was shown to be a relevant effect modifier in the consideration of subgroup results on the secondary composite outcome. There was no statistically significant result for this outcome for Europe and Latin America, whereas a statistically significant result in favour of evolocumab versus the comparator therapy was shown for North America and the Asian-Pacific region (Appendix A.2, Table 17). These heterogeneous results for the 2 largest subpopulations of the study, Europe and North America, were mainly caused by the results on the outcome components on cardiac events (myocardial infarction and cardiovascular death),

but hardly by cerebral events (see Appendix A.2, Figure 2). The advantage of evolocumab in comparison with placebo for the outcome "myocardial infarction" was notably more pronounced for North America than for Europe. A markedly higher rate of myocardial infarctions in the control arm of the subgroup of North America in comparison with Europe (7.4% versus 4.3%) was noted, which suggests a different quality of health care or a different baseline risk. The effects were even reversed for the outcome "cardiovascular death" (effect estimation in Europe to the disadvantage of evolocumab). This marked difference in the results on cardiovascular death of these 2 subgroups, which were not in the same direction, was also shown in the subgroup results on all-cause mortality (see Appendix A.2, Figure 3).

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 comparison with the ACT in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who are eligible for statin therapy. This resulted 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 presented no suitable data for patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who are eligible for statin therapy, an added benefit of evolocumab for these patients is not proven.

This deviates from the assessment of the company, which derived proof of considerable added benefit of evolocumab for patients at very high cardiovascular risk who are unable to reach LDL-C goals with the maximum tolerated dose of a statin.

2.3.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.4 Research question 2: patients who are not eligible for statin therapy

2.4.1 Information retrieval and study pool

The assessment of the added benefit of evolocumab as an adjunct to diet and possibly other lipid-lowering drugs compared with the ACT in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who are not eligible for statin therapy due to statin intolerance or contraindications was not part of the company's dossier. The company justified this with the lack of data that would be considered in a benefit assessment procedure. Hence, no data were available for a benefit assessment.

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 primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who are not eligible for statin therapy due to statin intolerance or contraindications. For this research question, this resulted 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 presented no data for patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who are not eligible for statin therapy due to statin intolerance or contraindications, an added benefit of evolocumab for this research question is not proven.

2.4.4 List of included studies

Not applicable as the company presented no data for the benefit assessment.

2.5 Research question 3: patients in whom drug and dietary options to reduce lipid levels have 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: 1 March 2018)
- bibliographical literature search on evolocumab (last search on 1 March 2018)
- search in trial registries for studies on evolocumab (last search on 1 March 2018)

To check the completeness of the study pool:

- search in trial registries for studies on evolocumab (last search on 21 March 2018)

No relevant study was identified from the check.

Study pool of the company

From the steps of information retrieval mentioned for research question 3, the company identified 1 randomized, active-controlled study (APHERESE [17]). This study was unsuitable to derive conclusions on the added benefit of evolocumab in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary options to reduce lipid levels have been exhausted. This was mainly due to the randomized study duration of only 6 weeks, which was too short. In addition, it was questionable whether the population of the APHERESE study concurs with the present research question. Both aspects are described in detail below.

The APHERESE study had a randomized phase of 6 weeks and 1 single-arm subsequent treatment phase with evolocumab of 18 weeks. It included patients who had received LDL apheresis for at least 3 months before screening. Homozygous familial hypercholesterolaemia was an exclusion criterion. A total of 39 patients were randomly allocated in a 1:1 ratio to evolocumab (administration every 2 weeks) or LDL apheresis (weekly or every 2 weeks), each in combination with lipid-lowering pharmacological background therapy. According to the study documents, the lipid-lowering pharmacological background therapy was to be continued without changes during the total duration of the APHERESE study. The study's primary goal was to investigate the effect of evolocumab on the possible avoidance of LDL apheresis after 4 weeks, operationalized as an LDL-C value of below 100 mg/dL after 4 weeks of treatment. In addition, the effect of evolocumab (or of the anticipated reduction of necessary LDL apheresis) on the change of the LDL-C value and on health-related quality of life was investigated. Side effects were also recorded.

Due to the short duration of the randomized study phase of only 6 weeks in total, the APHERESE study was unsuitable for the assessment of the added benefit of evolocumab. Evolocumab is intended for use in the long-term treatment of a chronic disease for cardiovascular risk reduction. Furthermore, the main goal of evolocumab therapy in the APHERESE study was the avoidance of LDL apheresis, which was linked to achieving a predefined LDL-C goal. Irrespective of the clinical relevance of this goal in the present population, studies of notably longer durations are required for the investigation of maintaining these goals for a long period of time and the possibility of continued avoidance of LDL apheresis. This particularly applies to the population investigated in the present research question, i.e. patients in whom drug and dietary options to reduce lipid levels have been exhausted and who hence present with refractory disease. An observation period of 6 weeks in the randomized comparison allows no conclusions on long-term treatment with evolocumab or with the comparator therapy (apheresis). Deviating from the company, and concurring with comparable procedures in the therapeutic indication [18,19] and with the G-BA's decision [20], a longer study duration is considered meaningful against the background of a long-term treatment also in this population to assess the long-term effects of evolocumab and of a reduction of LDL-C apheresis frequency on patient-relevant outcomes in the present benefit assessment (see Section 2.7.2.1 of the full dossier assessment).

Besides the decisive problem of the study duration that is too short, it is also questionable whether the population of the APHERESE study concurs with the present research question, which presupposes that LDL apheresis is used as last resort. The criterion that the patients were already receiving their individual maximum lipid-lowering therapy was no inclusion criterion of the study. It can be inferred from the study documents that 17.9% of the patients were not receiving any lipid-lowering drug therapy at all although they had not achieved their individual LDL-C target levels of below 100 mg/dL. 15.4% of the patients were receiving a statin therapy equivalent to less than 40 mg atorvastatin or less than 20 mg rosuvastatin. Although in these cases the physician had to justify why no higher dose was chosen, these justifications were not provided in the study documents. The company only stated for just over a third of the patients, i.e. those receiving "low intensity" or no statin therapy (38.5%), that they had statin intolerance. 46.2% of the patients were receiving a statin dose designated as "high-intensity statin therapy" in the study. This also included a statin dose of 40 mg atorvastatin, which only corresponds to half the possible maximum dose; hence a maximum tolerated dose cannot be assumed per se. Other lipid-lowering therapies administered were anion exchangers in 5.1% of the patients, fenofibrate in 17.9% and further lipid-lowering therapies in 61.5%, including ezetimibe in 51.3%. There was no information on whether these lipid-lowering drugs were administered alone, in addition to statin therapy or even in combination. As a consequence, LDL apheresis was therefore possibly not used as last resort in a relevant proportion of the patients, or the drug treatment was reduced in the meantime due to the ongoing LDL apheresis treatment. In the latter case, however, it would have been meaningful to allow escalation of drug treatment in the LDL apheresis arm because the aim of the APHERESE study was to evaluate the potential for reducing LDL apheresis treatments by escalating drug treatment, and for a fair comparison this would have been necessary also in the comparator arm.

2.5.2 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 (familial and non-familial) or mixed dyslipidaemia in whom drug and dietary lipid-lowering options have been exhausted. For this research question, this resulted 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 presented no suitable data for patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary lipid-lowering options have been exhausted, an added benefit of evolocumab for this research question is not proven. This deviates from the assessment of the company, which derived a hint of considerable added benefit of evolocumab for patients at (very) high cardiovascular risk.

2.5.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.6 Probability and extent of added benefit – summary

Table 5 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 5: Evolocumab – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Patients who are eligible for statin therapy[b]	Maximum tolerated drug and dietary treatment to reduce lipid levels	Added benefit not proven
Patients who are not eligible for statin therapy due to statin intolerance or contraindications	Lipid-lowering drugs other than statins (fibrates, anion exchangers, cholesterol resorption inhibitors) as monotherapy and dietary lipid-lowering therapy	Added benefit not proven
Patients in whom drug and dietary options to reduce lipid levels have been exhausted	LDL apheresis (as “last resort” in refractory disease)[c] possibly with concomitant lipid-lowering drug treatment	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive [4]. Not reaching LDL-C goals with the maximum tolerated dose of a statin is an additional precondition for an approval-compliant use of evolocumab [5]. c: It is a general precondition that LDL-C cannot be lowered sufficiently with documented maximum dietary and drug treatment for at least 12 months [6]. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low density lipoprotein; LDL-C: LDL cholesterol		

The G-BA decides on the added benefit.

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Please see full dossier assessment for full reference list.

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Appendix A – Supplementary presentation of the FOURIER study

A.1 Characteristics of the FOURIER study included by the company

Table 9: Characteristics of the study included by the company – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
FOURIER	RCT, double-blind, parallel	Adult patients (≥ 40 to ≤ 85 years) with cardiovascular disease[b], with ≥ 1 major[c] or ≥ 2 other[d] risk factors, and increased LDL-C (≥ 70 mg/dL) or non-HDL-C (≥ 100 mg/dL) values under stable lipid-lowering therapy	In each case in combination with individually optimized statin dose ± ezetimibe: evolocumab (N = 13 784) placebo (N = 13 780)	▪ Screening: up to 15 weeks (titration of the lipid-lowering therapy and placebo run-in) ▪ Treatment: event-driven, until occurrence of 1630 events of the secondary composite key outcome (end of study): cardiovascular death, MI or stroke ▪ Observation: until death, discontinuation of participation in the study or at most until end of study[e]	1242 study centres in 49 countries in Europe, North America, Asia-Pacific and Latin America Feb 2013–Jan 2017	Primary: composite outcome: time to cardiovascular death (including fatal MI and fatal stroke), nonfatal MI, nonfatal stroke, hospitalization for unstable angina pectoris or coronary revascularization Secondary: mortality, cardiovascular events, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes from the information provided by the company in Module 4 of the dossier.
b: Clinically evident cardiovascular disease included prior MI, non-haemorrhagic stroke and symptomatic peripheral arterial occlusive disease.
c: Major risk factors are: type 1 or 2 diabetes mellitus, age ≥ 65 years, MI or non-haemorrhagic stroke within 6 months before screening, additional diagnosis of an MI or of a non-haemorrhagic stroke except for the qualifying event, current smoking (daily), history of symptomatic peripheral arterial occlusive disease.
d: Other risk factors are: history of coronary revascularization for other reasons than MI, coronary heart disease with ≥ 40% stenosis in ≥ 2 large vessels, male patients with HDL-C < 40 mg/dL and female patients with HDL-C < 50 mg/dL at screening, hsCRP > 2.0 mg/L at screening, final LDL-C ≥ 130 mg/dL or non-HDL-C ≥ 160 mg/dL at screening, metabolic syndrome (defined by ≥ 3 of the following criteria: waist circumference in men > 102 cm and in women > 88 cm, triglyceride level ≥ 150 mg/dL at screening, HDL-C for men < 40 mg/dL and for women < 50 mg/dL at screening [note: if the HDL-C value is used as criterion for the diagnosis of the metabolic syndrome, it cannot be used as separate risk factor], blood pressure ≥ 130/85 mmHg or drug treatment for blood pressure, fasting blood glucose ≥ 110 mg/dL at screening).
e: AEs were followed up for 30 days (+ 7 days) after the end of study (safety follow-up).
AE: adverse event; HDL: high-density lipoprotein; HDL-C: HDL cholesterol; hsCRP: high-sensitivity C-reactive protein; LDL: low density lipoprotein; LDL-C: LDL cholesterol; MI: myocardial infarction; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 10: Characteristics of the intervention – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

<table>
<tr><th>Study</th><th>Intervention</th><th>Comparison</th></tr>
<tr><td rowspan="4">FOURIER</td><td colspan="2">Screening phase (about 15 weeks maximum):
▪ Titration of the lipid-lowering background therapy before start of study (randomization) for patients who, in the opinion of the physician, have not yet received optimum lipid-lowering therapy, in compliance with the CPGs of the local professional societies:
▫ adjustment of the optimum statin dose: at least atorvastatin 20 mg QD or equivalent (simvastatin 40 mg, rosuvastatin 5 mg, pitavastatin 4 mg)[a], if locally approved ≥ 40 mg atorvastatin[b] or equivalent (simvastatin 80 mg, rosuvastatin 10 mg, 20 mg, 40 mg)[a] recommended
▫ ezetimibe and further lipid-lowering drugs were not required, but could be administered in addition to statin therapy (except non-permitted concomitant treatments)</td></tr>
<tr><td colspan="2">Treatment phase (up to 5 years)
Evolocumab (subcutaneous, using pre-filled pen):[c]
▪ 140 mg, Q2W or 420 mg, QM
▪ no dose adjustment allowed
+
Placebo (subcutaneous, using pre-filled pen):[c]
▪ Q2W or QM
▪ no dose adjustment allowed
+
▪ Continued lipid-lowering background therapy according to screening phase, unchanged during total study duration. Only additional administration of ezetimibe (10 mg QD) after randomization could be considered on occurrence of an acute coronary syndrome after consultation with the Amgen Medical Monitor or representative.</td></tr>
<tr><td colspan="2">Allowed prior and concomitant treatment:
▪ cholesterol-lowering diet[d] before the start of the study and during the study
▪ preparations that influence lipid levels at a stable dose for ≥ 2 weeks before final screening (e.g. psyllium preparations, plant stanols, niacin, omega-3 fatty acids, fenofibrate[e])
▪ any necessary concomitant medication
Non-permitted concomitant treatment
▪ other PCSK9 inhibitors
▪ mipomersen, lomitapide, fibrates and derivatives except fenofibrate[e]
▪ any lipid-lowering therapies that were not taken at the time point of randomization</td></tr>
<tr><td colspan="3">a: Other statins than the ones mentioned here were not to be used.
b: For patients with LDL-C > 100 mg/dL before randomization who were not treated with a dose of ≥ 40 mg atorvastatin (or equivalent), the investigator had to confirm that a higher dose was inadequate (e.g. refusal of patient, intolerance of higher dose, dose not available in the respective country, other important concerns).
c: Based on preference, the study participants had the possibility every 12 weeks to switch between both dosages at an interval (Q2W/QM).
d: Diet according to NCEP ATP III TLC or equivalent.
e: Treatment with fenofibrate had to be unchanged for at least 6 weeks before randomization in an optimized dose unchanged for the total study duration.
CPG: clinical practice guideline; LDL: low density lipoprotein; LDL-C: LDL cholesterol; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; Q2W: every 2 weeks (± 3 days); QD: daily; QM: every 4 weeks (± 3 days); RCT: randomized controlled trial; TLC: therapeutic lifestyle changes; vs.: versus</td></tr>
</table>

Table 11: Characteristics of the study population – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study Characteristics Category	**Evolocumab + lipid-lowering therapy**	**Placebo + lipid-lowering therapy**
FOURIER	N[a] = 13 784	N[a] = 13 780
Age [years], mean (SD)	63 (9)	63 (9)
Sex [F/M], %	25/75	25/75
Geographical region, n (%)		
Europe	8666 (63)	8669 (63)
North America	2287 (17)	2284 (17)
Latin America	913 (7)	910 (7)
Asia-Pacific[b]	1918 (14)	1917 (14)
LDL-C at baseline [mg/dL], mean (SD)	97.8 (28.9)	97.6 (27.1)
Cardiovascular events before randomization, n (%)		
Myocardial infarction	11 145 (81)	11 206 (81)
Non-haemorrhagic stroke	2686 (20)	2651 (19)
Symptomatic PAOD	1858 (14)	1784 (13)
≥ 1 cardiovascular event	13 774 (99.9)	13 773 (99.9)
2 cardiovascular events	1679 (12)	1664 (12)
3 cardiovascular events	118 (1)	102 (1)
Type 1 diabetes mellitus, n (%)	154 (1)	140 (1)
Type 2 diabetes mellitus, n (%)	4904 (36)	4891 (36)
Chronic kidney disease[c], n (%)	854 (6)	809 (6)
Treatment discontinuation, n (%)	1682 (12)	1746 (13)
Study discontinuation, n (%)	93 (1)	118 (1)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding column if the deviations are relevant.
b: India, Australia, New Zealand and South Africa are also included besides Asia.
c: Glomerular filtration rate < 60 mL/min per 1.73 m^3 for ≥ 3 months.

LDL: low density lipoprotein; LDL-C: LDL cholesterol; F: female; M: male; n: number of patients in the category; N: number of randomized patients; PAOD: peripheral arterial occlusive disease; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 12: Lipid-lowering background therapy at baseline – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study **Characteristics** **Category** **Drug**	**Evolocumab + lipid-lowering therapy**	**Placebo + lipid-lowering therapy**
FOURIER	N[a] = 13 784	N[a] = 13 780
Statin treatment, n (%)		
Atorvastatin 20 mg or equivalent[b]	3550 (25.8)	3567 (25.9)
Atorvastatin 40 mg or equivalent[c]	5364 (38.9)	5343 (38.8)
Atorvastatin 80 mg or equivalent[d]	4053 (29.4)	4060 (29.5)
Other statins	85 (0.6)	92 (0.7)
Any statin + ezetimibe	725 (5.3)	711 (5.2)
Other lipid-lowering therapy, n (%)		
Anion exchangers	13 (< 0.1)	16 (0.1)
Fibrates	362 (2.6)	382 (2.8)
Nicotinic acid and derivatives	76 (0.6)	63 (0.5)
Other	1069 (7.8)	1095 (7.9)
Ezetimibe	726 (5.3)	714 (5.2)
Lipid-lowering therapy without statin	2 (< 0.1)	4 (< 0.1)
No lipid-lowering therapy	5 (< 0.1)	3 (< 0.1)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding column if the deviations are relevant.
b: Simvastatin 40 mg, rosuvastatin 5 mg, pitavastatin 4 mg are equivalent.
c: Simvastatin 80 mg, rosuvastatin 10 mg are equivalent.
d: Rosuvastatin 20 mg and 40 mg are equivalent.
n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 13: Information on the course of the study – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study **Duration of the study phase** **Outcome category**	**Evolocumab + lipid-lowering therapy**	**Placebo + lipid-lowering therapy**
FOURIER	N = 13 769	N = 13 756
Treatment duration [months][a]		
Median [Q1; Q3]	24.8 [19.5; 30.1]	24.7 [19.4; 30.2]
Mean (SD)	24.2 (8.2)	24.1 (8.3)
Observation period [months]		
Overall survival, morbidity, side effects		
Median [Q1; Q3]	26.0 [21.7; 30.4]	26.0 [21.7; 30.4]
Mean (SD)	26.1 (6.4)	26.1 (6.4)

a: Defined as duration of exposure to the investigational preparation.

N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

A.2 Results of the FOURIER study

Table 14: Results (mortality, morbidity) – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study Outcome category Outcome	Evolocumab + lipid-lowering therapy N	Evolocumab + lipid-lowering therapy Median time to event in months [95% CI] Patients with event n (%)	Placebo + lipid-lowering therapy N	Placebo + lipid-lowering therapy Median time to event in months [95% CI] Patients with event n (%)	Evolocumab vs. placebo HR [95% CI][a]; p-value[b]
FOURIER					
Mortality					
All-cause mortality	13 784	NA 444 (3.2)	13 780	NA 426 (3.1)	1.04 [0.91; 1.19]; 0.537
Morbidity					
Composite outcome: cardiovascular death, MI or stroke[c]	13 784	NA 816 (5.9)	13 780	NA 1013 (7.4)	0.80 [0.73; 0.88]; < 0.001
Cardiovascular death[d]	13 784	NA 251 (1.8)	13 780	NA 240 (1.7)	1.05 [0.88; 1.25]; 0.619
Fatal or nonfatal MI	13 784	NA 468 (3.4)	13 780	NA 639 (4.6)	0.73 [0.65; 0.82]; < 0.001
Fatal MI	13 784	NA 23 (0.2)	13 780	NA 27 (0.2)	0.85 [0.49; 1.49]; 0.571
Nonfatal MI	13 784	NA 448 (3.3)	13 780	NA 616 (4.5)	0.72 [0.64; 0.82]; < 0.001
Fatal or nonfatal stroke	13 784	NA 207 (1.5)	13 780	NA 262 (1.9)	0.79 [0.66; 0.95]; 0.010
Fatal stroke	13 784	NA 35 (0.3)	13 780	NA 33 (0.2)	1.06 [0.66; 1.71]; 0.810
Nonfatal stroke	13 784	NA 176 (1.3)	13 780	NA 231 (1.7)	0.76 [0.62; 0.92]; 0.006
TIA	13 784	NA 61 (0.4)	13 780	NA 76 (0.6)	0.80 [0.57; 1.12]; 0.197
Hospitalization for unstable angina pectoris	13 784	NA 236 (1.7)	13 780	NA 239 (1.7)	0.99 [0.82; 1.18]; 0.889
Hospitalization for worsening of cardiac failure	13 784	NA 194 (1.4)	13 780	NA 201 (1.5)	0.96 [0.79; 1.17]; 0.715
Health-related quality of life					
Outcome not recorded					

(continued)

Table 14: Results (mortality, morbidity) – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy (continued)

a: Based on a Cox proportional hazards model stratified by LDL-C value at final screening (< 85 mg/dL vs. ≥ 85 mg/dL) and geographical region.
b: 2-sided log-rank test stratified by LDL-C value at final screening (< 85 mg/dL vs. ≥ 85 mg/dL) and geographical region.
c: Only the event that occurred first is counted.
d: Defined as one of the following events: acute MI, sudden cardiac death, stroke, death due to cardiovascular interventions, cardiovascular bleeding, other causes with specific cardiovascular connection (e.g. pulmonary embolism or peripheral arterial occlusive disease).

CI: confidence interval; HR: hazard ratio; LDL: low density lipoprotein; LDL-C: LDL cholesterol; MI: myocardial infarction; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; TIA: transient ischaemic attack; vs.: versus

Table 15: Results (side effects) – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study **Outcome category**	**Evolocumab + lipid-lowering therapy**		**Placebo + lipid-lowering therapy**		**Evolocumab vs. placebo**
Outcome	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
FOURIER					
Side effects					
AEs (additional information)	13 769	10 664 (77.4)	13 756	10 644 (77.4)	Not applicable
SAEs	13 769	3 410 (24.8)	13 756	3 404 (24.7)	1.00 [0.96; 1.04]; 0.979
Discontinuation due to AEs	13 769	608 (4.4)	13 756	573 (4.2)	1.06 [0.95; 1.19]; 0.312

a: Institute's calculation, unconditional exact test (CSZ method according to [21]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 16: Results (supplementary outcome: LDL-C at week 120) – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study Outcome category Outcome	Evolocumab + lipid-lowering therapy			Placebo + lipid-lowering therapy			Evolocumab vs. placebo
	N[a]	Values at baseline mean (SD)	Change at week 120 mean (SE)	N[a]	Values at baseline mean (SD)	Change at week 120 mean (SE)	MD [95% CI]; p-value[b]
FOURIER							
Supplementary outcome							
LDL-C at week 120 (mg/dL)	13 784	97.8 (28.9)	−53.4 (0.5)	13 780	97.6 (27.1)	0.6 (0.4)	−52.2 [−53.2; −51.2]; < 0.001

a: Number of patients with values at baseline, the analysis may be based on other patient numbers.
b: Effect, CI and p-value: MMRM on the change from baseline to end of study, adjusted for LDL-C value at final screening (< 85 mg/dL vs. ≥ 85 mg/dL) and geographical region.

CI: confidence interval; LDL: low-density lipoprotein; LDL-C: LDL cholesterol; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

A.2.1 Results on selected subgroups

Table 17: Subgroup "region" (morbidity) – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study Outcome Characteristic Subgroup	Evolocumab + lipid-lowering therapy N	Median time to event in months [95% CI] Patients with event n (%)	Placebo + lipid-lowering therapy N	Median time to event in months [95% CI] Patients with event n (%)	Evolocumab vs. placebo HR [95% CI][a]	p-value
FOURIER						
Composite outcome: cardiovascular death, myocardial infarction or stroke[b]						
Geographical region						
Europe	8666	NA 522 (6.0)	8669	NA 580 (6.7)	0.90 [0.80; 1.01]	0.070[c]
North America	2287	NA 153 (6.7)	2284	NA 241 (10.6)	0.62 [0.51; 0.76]	< 0.001[c]
Latin America	913	NA 50 (5.5)	910	NA 58 (6.4)	0.85 [0.58; 1.24]	0.403[c]
Asia-Pacific	1918	NA 91 (4.7)	1917	NA 134 (7.0)	0.67 [0.51; 0.88]	0.003[c]
Total					Interaction:	0.012[d]

a: Based on a Cox proportional hazards model stratified by LDL-C value at final screening (< 85 mg/dL vs. ≥ 85 mg/dL).
b: Only the event that occurred first is counted.
c: 2-sided log-rank test stratified by LDL-C value at final screening.
d: Based on a Cox proportional hazards model with subgroups and subgroup-treatment interaction.
CI: confidence interval; HR: hazard ratio; LDL: low density lipoprotein; LDL-C: LDL cholesterol; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; vs.: versus

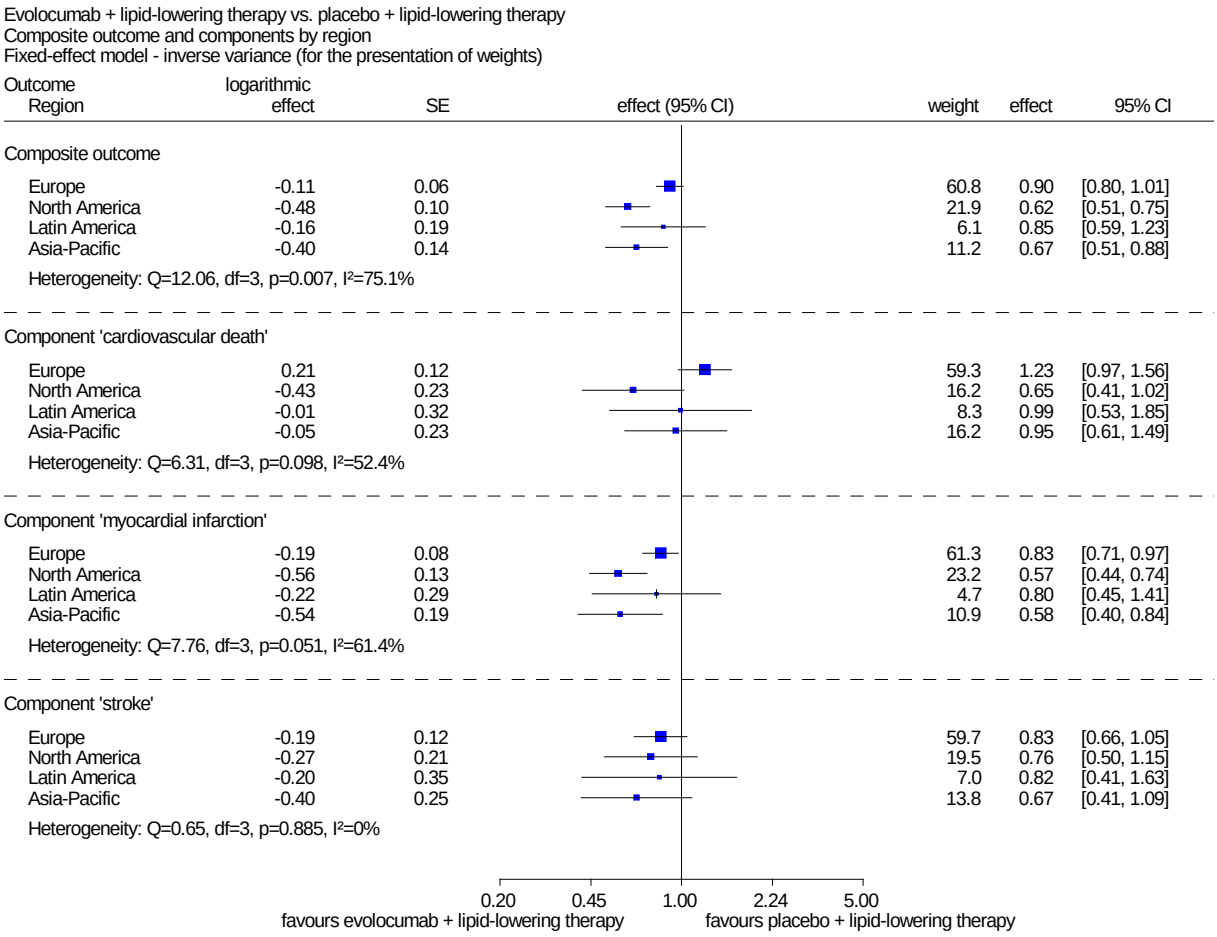

Figure 2: Results on the composite outcome and on the individual components on the comparison of evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy according to the subgroup characteristic “region” in the FOURIER study; effect measure hazar

There were small deviations in comparison with the results of the company regarding the heterogeneity shown in the figure because the model was based only on the overall estimators, but not on the individual patient data.

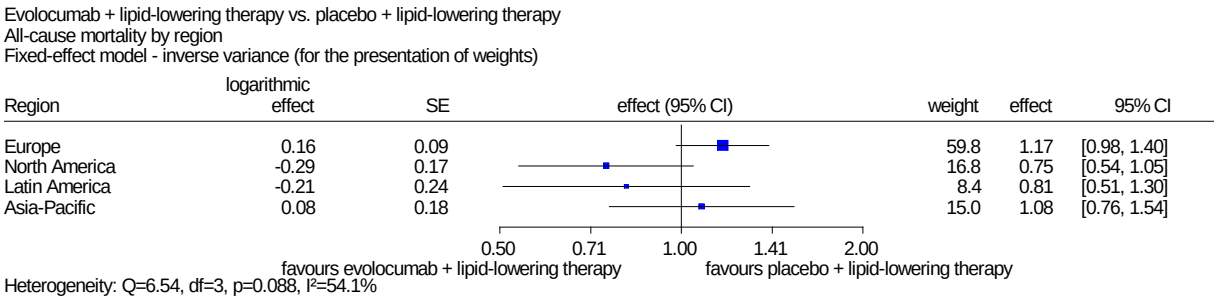

Figure 3: Results on all-cause mortality on the comparison of evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy according to the subgroup characteristic "region" in the FOURIER study; effect measure hazard ratio (Institute's calculation)

There were small deviations in comparison with the results of the company regarding the heterogeneity shown in the figure because the model was based only on the overall estimators, but not on the individual patient data.

A.2.2 Common adverse events, serious adverse events and discontinuations due to adverse events

Table 18: Common AEs (in the SOC or in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study	Patients with event n (%)	
SOC[a] PT[a]	Evolocumab + lipid-lowering therapy N = 13 769	Placebo + lipid-lowering therapy N = 13 756
FOURIER		
Overall rate of AEs	10 664 (77.4)	10 644 (77.4)
Blood and lymphatic system disorders	459 (3.3)	482 (3.5)
Cardiac disorders	1885 (13.7)	1948 (14.2)
Angina pectoris	472 (3.4)	536 (3.9)
Ear and labyrinth disorders	408 (3.0)	402 (2.9)
Eye disorders	573 (4.2)	615 (4.5)
Gastrointestinal disorders	2393 (17.4)	2381 (17.3)
Diarrhoea	469 (3.4)	430 (3.1)
General disorders and administration site conditions	1910 (13.9)	1941 (14.1)
Infections and infestations	4857 (35.3)	4775 (34.7)
Influenza	472 (3.4)	419 (3.0)
Bronchitis	573 (4.2)	561 (4.1)
Nasopharyngitis	1068 (7.8)	1021 (7.4)
Upper respiratory tract infection	698 (5.1)	655 (4.8)
Urinary tract infection	584 (4.2)	558 (4.1)
Injury, poisoning and procedural complications	1458 (10.6)	1458 (10.6)
Investigations	1240 (9.0)	1165 (8.5)
Metabolism and nutrition disorders	2527 (18.4)	2427 (17.6)
Diabetes mellitus	1207 (8.8)	1130 (8.2)
Musculoskeletal and connective tissue disorders	3350 (24.3)	3354 (24.4)
Arthralgia	605 (4.4)	589 (4.3)
Myalgia	555 (4.0)	527 (3.8)
Back pain	673 (4.9)	651 (4.7)
Pain in extremity	428 (3.1)	451 (3.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	622 (4.5)	621 (4.5)
Nervous system disorders	2125 (15.4)	2253 (16.4)
Headache	440 (3.2)	508 (3.7)
Dizziness	474 (3.4)	435 (3.2)

(continued)

Table 18: Common AEs (in the SOC or in the PT ≥ 3% in at least one study arm) – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy (continued)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Evolocumab + lipid-lowering therapy N = 13 769**	**Placebo + lipid-lowering therapy N = 13 756**
FOURIER		
Psychiatric disorders	755 (5.5)	750 (5.5)
Renal and urinary disorders	900 (6.5)	916 (6.7)
Reproductive system and breast disorders	458 (3.3)	449 (3.3)
Respiratory, thoracic and mediastinal disorders	1695 (12.3)	1737 (12.6)
Cough	436 (3.2)	468 (3.4)
Skin and subcutaneous tissue disorders	1059 (7.7)	1041 (7.6)
Vascular disorders	1995 (14.5)	2030 (14.8)
Hypertension	1108 (8.0)	1190 (8.7)

a: MedDRA version 19.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 19: Common SAEs (in the SOC or in the PT ≥ 0.5% in at least one study arm) – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Evolocumab + lipid-lowering therapy N = 13 769**	**Placebo + lipid-lowering therapy N = 13 756**
FOURIER		
Overall rate of SAEs	3410 (24.8)	3404 (24.7)
Cardiac disorders	941 (6.8)	998 (7.3)
Cardiac failure	66 (0.5)	66 (0.5)
Angina unstable	233 (1.7)	278 (2.0)
Angina pectoris	208 (1.5)	221 (1.6)
Atrial fibrillation	119 (0.9)	132 (1.0)
Gastrointestinal disorders	366 (2.7)	370 (2.7)
General disorders and administration site conditions	207 (1.5)	222 (1.6)
Non-cardiac chest pain	109 (0.8)	133 (1.0)
Hepatobiliary disorders	120 (0.9)	91 (0.7)
Infections and infestations	568 (4.1)	584 (4.2)
Pneumonia	147 (1.1)	152 (1.1)
Injury, poisoning and procedural complications	284 (2.1)	271 (2.0)
Investigations	98 (0.7)	75 (0.5)
Metabolism and nutrition disorders	159 (1.2)	156 (1.1)
Musculoskeletal and connective tissue disorders	353 (2.6)	347 (2.5)
Osteoarthritis	91 (0.7)	100 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	348 (2.5)	328 (2.4)
Nervous system disorders	351 (2.5)	365 (2.7)
Syncope	63 (0.5)	56 (0.4)
Psychiatric disorders	60 (0.4)	66 (0.5)
Renal and urinary disorders	178 (1.3)	179 (1.3)
Acute kidney injury	64 (0.5)	64 (0.5)
Respiratory, thoracic and mediastinal disorders	222 (1.6)	231 (1.7)
Chronic obstructive pulmonary disease	64 (0.5)	64 (0.5)
Vascular disorders	376 (2.7)	364 (2.6)
Peripheral arterial occlusive disease	94 (0.7)	82 (0.6)

a: MedDRA version 19.1.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 20: Common AEs leading to treatment discontinuation (in the SOC or in the PT ≥ 0.1% events in at least one study arm) – RCT, direct comparison: evolocumab + lipid-lowering therapy vs. placebo + lipid-lowering therapy

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Evolocumab + lipid-lowering therapy N = 13 769**	**Placebo + lipid-lowering therapy N = 13 756**
FOURIER		
Overall rate of discontinuations due to AEs	608 (4.4)	573 (4.2)
Cardiac disorders	29 (0.2)	37 (0.3)
Eye disorders	14 (0.1)	5 (< 0.1)
Gastrointestinal disorders	46 (0.3)	57 (0.4)
General disorders and administration site conditions	62 (0.5)	69 (0.5)
Fatigue	12 (< 0.1)	23 (0.2)
Hepatobiliary disorders	19 (0.1)	8 (< 0.1)
Infections and infestations	45 (0.3)	39 (0.3)
Injury, poisoning and procedural complications	25 (0.2)	15 (0.1)
Investigations	46 (0.3)	31 (0.2)
Metabolism and nutrition disorders	10 (< 0.1)	15 (0.1)
Musculoskeletal and connective tissue disorders	105 (0.8)	103 (0.7)
Arthralgia	14 (0.1)	13 (< 0.1)
Myalgia	37 (0.3)	46 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	114 (0.8)	105 (0.8)
Nervous system disorders	65 (0.5)	72 (0.5)
Renal and urinary disorders	13 (< 0.1)	18 (0.1)
Respiratory, thoracic and mediastinal disorders	16 (0.1)	23 (0.2)
Skin and subcutaneous tissue disorders	53 (0.4)	44 (0.3)
Vascular disorders	20 (0.1)	26 (0.2)

a: MedDRA version 19.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-19-evolocumab-primary-hypercholesterolaemia-or-mixed-dyslipidaemia-benefit-assessment-according-to-35a-social-code-book-v-new-scientific-findings.9392.html.