IQWiG Reports – Commission No. A16-16

Alirocumab – Addendum to Commission A15-47[1]

Addendum

Commission: A16-16
Version: 1.0
Status: 14 April 2016

[1] Translation of addendum A16-16 *Alirocumab – Addendum zum Auftrag A15-47* (Version 1.0; Status: 14 April 2016). 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Alirocumab – Addendum to Commission A15-47

Commissioning agency:
Federal Joint Committee

Commission awarded on:
22 March 2016

Internal Commission No.:
A16-16

Address of publisher:
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Keywords: alirocumab, hypercholesterolemia, benefit assessment

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

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Abbreviation	Meaning
AE	adverse event
CK	creatine kinase
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDL	low-density lipoprotein
LDL-C	LDL cholesterol
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
W-BQ22	Well-Being Questionnaire with 22 items

1 Background

On 22 March 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-47 (Alirocumab – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In the framework of the commenting procedure for the benefit assessment of alirocumab, the company subsequently submitted data on research questions A (patients for whom statins are a treatment option) and C (patients in whom drug and dietary lipid-lowering options have been exhausted). On the one hand, the company submitted new analyses on the COMBO II study already known from the dossier [2] (research question A) [3,4], on the other, it submitted a first analysis of the results of the ESCAPE study (research question C) [5-7].

To be able to make a decision on the added benefit of alirocumab, the G-BA commissioned IQWiG with the assessment of the studies COMBO II and ESCAPE.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Research question A (patients for whom statins are a treatment option)

2.1 Analyses subsequently submitted

In its dossier, the company had presented a total of 9 studies on research question A (patients for whom statins are a treatment option). None of the 9 studies was suitable for the benefit assessment [1]. COMBO II was one of these 9 studies [8]. The COMBO II study was the only one of the 9 studies in which both treatment escalation within the comparator group was conducted (additional administration of ezetimibe) and treatment and observation period were sufficiently long (at least one year). However, it could not be assumed for the majority of the patients included in the COMBO II study that they had been pretreated with the maximum tolerated dose of a statin. This was the prerequisite for the approval-compliant use of alirocumab, however, and for the suitability for research question A of the benefit assessment.

With its written comments, the company presented an analysis of the COMBO II study that only included those patients for whom, according to the company, a maximum tolerated dose of a statin could be assumed [4]. The assessment of the results on this subpopulation is subject of the following sections.

2.2 Study design and study characteristics

The following tables Table 1 and Table 2 describe the characteristics of the COMBO II study. Table 3 contains the characteristics of the relevant subpopulation of the COMBO II study.

Table 1: Characteristics of the study – COMBO II: alirocumab + statin vs. ezetimibe + statin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
COMBO II	RCT, double-blind, parallel	Adult HC patients at very high cardiovascular risk[b] with inadequately controlled LDL-C under statin treatment 4 weeks before screening	Each in combination with a statin alirocumab (N = 479) ezetimibe (N = 241) Relevant subpopulation thereof[c]: alirocumab (n = 172) ezetimibe (n = 87)	▪ Screening: 3 weeks ▪ Treatment: 104 weeks ▪ Follow-up: 8 weeks	126 study centres in Canada, Denmark, France, Hungary, Israel, Russia, South Africa, South Korea, Ukraine, USA 8/2012 – 7/2015	Primary: change in LDL-C value Secondary: mortality, cardiovascular events, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Very high cardiovascular risk is defined as patients with coronary heart disease (acute or silent myocardial infarction, unstable angina pectoris, coronary revascularization procedure, diagnosis of other clinically relevant coronary heart disease) or other risk factors (peripheral arterial occlusive disease, ischaemic stroke, moderate renal insufficiency, type 1 or 2 diabetes mellitus and at least 2 additional risk factors) with LDL-C value ≥ 70 mg/dL.
c: Maximum tolerated dose of a statin: 80 mg atorvastatin or 40 mg rosuvastatin or 80 mg simvastatin or treatment with a lower daily dose of a statin due to AEs (muscle symptoms and/or increased CK levels).

AE: adverse event; CK: creatine kinase; HC: hypercholesterolaemia; LDL: low-density lipoprotein; LDL-C: LDL cholesterol; n: number of patients in the relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 2: Characteristics of the interventions – COMBO II: alirocumab + statin vs. ezetimibe + statin

Study	Intervention	Comparison
COMBO II	Alirocumab 75 mg Q2W, SC, from randomization to week 12 Dose adjustment: 75 mg or 150 mg Q2W, SC, from week 12 until week 102; up-titration to 150 mg if LDL-C value ≥ 70 mg/dL in week 8 + placebo for ezetimibe, once daily, orally, from randomization until week 104	Ezetimibe 10 mg once daily, orally, from randomization until week 104 no dose adjustment allowed + placebo for alirocumab, Q2W, SC, from randomization until week 102
	Basic therapy[a]: ▪ rosuvastatin, atorvastatin or simvastatin, at a stable dosage from 4 weeks before the start of the study until the end of the follow-up phase ▪ stable cholesterol-lowering diet[b] before the start of the study and during the study	
	Prohibited prior and concomitant treatment: ▪ statins other than rosuvastatin, atorvastatin or simvastatin ▪ cholesterol absorption inhibitors (i.e. ezetimibe), omega-3 fatty acids (at a dosage of > 1000 mg/day), nicotinic acid, sequestrants, or red yeast rice products from 4 weeks before the start of the study ▪ fibrates, from 6 weeks before the start of the study ▪ dietary supplements or over-the-counter drugs that may influence blood lipid levels and that were not administered at a stable dose until at least 4 weeks before the start of the study ▪ plasmapheresis within 2 months before or during the study	

a: for relevant subpopulation, maximum tolerated dose of a statin: 80 mg atorvastatin or 40 mg rosuvastatin or 80 mg simvastatin or treatment with a lower daily dose of a statin due to AEs (muscle symptoms and/or increased CK levels).
b: Diet according to NCEP ATP III TLC or equivalent.

CK: creatine kinase; LDL: low-density lipoprotein; LDL-C: LDL cholesterol; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; Q2W: every 2 weeks; RCT: randomized controlled trial; SC: subcutaneously; TLC: therapeutic lifestyle changes; vs.: versus

Table 3: Characteristics of the study population – COMBO II: alirocumab + statin vs. ezetimibe + statin

Study Characteristics Category	**Alirocumab + statin N[a] = 172**	**Ezetimibe + statin N[a] = 87**
COMBO II		
Age [years], mean (SD)	62 (9)	60 (9)
Sex [F/M], %	21/79	23/77
LDL-C at baseline [mg/dL], mean (SD)	99.8 (29.8)	102.6 (31.3)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	ND	ND
Ethnicity, n (%)		
White	165 (95.9)	78 (89.7)
Black or African American	4 (2.3)	5 (5.7)
Asian	1 (0.6)	3 (3.4)
Other	2 (1.2)	1 (1.1)
Cardiovascular risk factors, n (%)	171 (99.4)	87 (100)
Coronary heart disease[b]	158 (91.9)	80 (92.0)
Other cardiovascular risk factors[c]	55 (32.0)	20 (23.0)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Acute or silent myocardial infarction, unstable angina pectoris, coronary revascularization procedure, or other clinically significant coronary heart disease.
c: Ischaemic stroke, peripheral arterial occlusive disease, moderate chronic renal insufficiency, diabetes mellitus and at least 2 additional risk factors (ankle-brachial index of ≤ 0.90, hypertension, microalbuminuria, macroalbuminuria, or a urinary dipstick result of > 2+ protein at baseline, preproliferative or proliferative retinopathy or laser treatment for retinopathy, or a family history of premature coronary heart disease).
F: female; LDL: low-density lipoprotein; LDL-C: LDL cholesterol; M: male; n: number of patients in the category; N: number of randomized patients in the relevant subpopulation; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

COMBO II was a randomized controlled trial (RCT). It was conducted in over 100 different centres worldwide, none of which was based in Germany. Adult patients at high cardiovascular risk who had not reached sufficient lowering of their LDL-C level on their prior therapy were included in the study. More than 90% of the patients already had known coronary heart disease. The mean low-density lipoprotein cholesterol (LDL-C) level at the start of the study was about 100 mg/dL. According to the approval, alirocumab is an option only for patients unable to reach LDL-C goals, i.e. only for patients treated with a treat-to-target strategy. Partly patients with an LDL-C value below 70 mg/dL were also included in the COMBO II study.

The patients received alirocumab or ezetimibe in addition to their ongoing statin treatment. The classification of the relevant subpopulation conducted by the company in the comment

(pretreatment with maximum tolerated dose of a statin) was adequate: The subpopulation only comprised those patients who had either been treated with the maximum dose of a statin or in whom only a lower dose of a statin could be used due to muscle symptoms and/or increased creatine kinase (CK) levels. These were only about 36% of the patients included in the COMBO II study. The criterion "lower statin dose due to muscle symptoms and/or increased CK" only applied to 8% of the patients included in the COMBO II study. Overall, this confirmed the assessment described in the dossier assessment on alirocumab: The inclusion criteria used in the COMBO II study were unsuitable to mainly include patients with an individual maximum tolerated dose of a statin. Hence only the subpopulation subsequently submitted by the company with the comments was relevant for the present assessment.

2.3 Results

Data cut-offs and data availability

Two dates of analysis were planned for the COMBO II study:

1) interim analysis after an observation period of 52 weeks (primary analysis for the approval of alirocumab)
2) analysis after the end of the study (after a treatment duration of 104 weeks + follow-up of 8 weeks)

The interim analysis after 52 weeks was based on a data cut-off in May 2014. According to the entry in the ClinicalTrials.gov trial registry, the COMBO II study was completed as planned in July 2015 [9]. Nonetheless, the company only presented an analysis for the subpopulation at the time point of 52 weeks with its comment. Whereas this was comprehensible for the original dossier due to the requirements described in the G-BA's rules of procedure [10], this was not adequate for the analyses subsequently submitted with the comments in March 2016. This applies all the more as the company even presented an analysis for the ESCAPE study only completed in January 2016 in the commenting procedure.

Risk of bias

The risk of bias of the COMBO II study at study level was rated as low. Due to the selective reporting of results only at week 52, there was an outcome-specific high risk of bias for all outcomes.

Results

The results of the COMBO II study are presented in Table 4 and Table 5. The results on the lowering of LDL-C levels, which constituted a non-validated surrogate outcome in the present constellation, are presented as additional information.

Table 4: Results (dichotomous outcomes) – COMBO II: alirocumab + statin vs. ezetimibe + statin

Study **Outcome category** *Time point* Outcome	**Alirocumab + statin**		**Ezetimibe + statin**		**Alirocumab vs. ezetimibe**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
COMBO II					
Mortality					
Results after week 104: The company did not present results after week 104					
Results after week 52:					
All-cause mortality[a]	172	1 (0.6)	87	1 (1.1)	0.51 [0.03; 7.99]; 0.621[b]
Morbidity					
Results after week 104: The company did not present results after week 104					
Results after week 52:					
Cardiovascular events (adjudicated, from recording of AEs)	172	8 (4.7)	87	4 (4.6)	1.20 [0.44; 3.30]; 0.723[b]
CHD death[c]	172	1 (0.6)	87	0 (0)	ND; 0.572[d]
Nonfatal MI	172	3 (1.7)	87	1 (1.1)	ND; 0.791[d]
Fatal/nonfatal ischaemic stroke[e]	172	0 (0)	87	0 (0)	ND; > 0.999[d]
Unstable angina requiring hospitalization	172	1 (0.6)	87	0 (0)	ND; 0.572[d]
Cardiac failure requiring hospitalization	172	0 (0)	87	1 (1.1)	ND; 0.175[d]
Ischaemia-driven coronary revascularization procedure	172	7 (4.1)	87	3 (3.4)	ND; 0.851[d]
Side effects					
Results after week 104: The company did not present results after week 104					
Results after week 52:					
AEs (supplementary information)	172	136 (79.1)	87	65 (74.7)	–
SAEs	172	35 (20.3)	87	19 (21.8)	0.93 [0.57; 1.53]; 0.780[b]
Discontinuation due to AEs	172	14 (8.1)	87	7 (8.0)	1.01 [0.42; 2.41]; 0.979[b]
General allergic reactions and injection site reactions	172	18 (10.5)	87	3 (3.4)	ND; 0.053[d]

a: Number of AEs leading to death during treatment.
b: Chi-square test.
c: Including death from unknown cause.
d: Institute's calculation, unconditional exact test (CSZ method according to [11]).
e: Including stroke not otherwise specified.

AE: adverse event; CI: confidence interval; CHD: coronary heart disease; CSZ: convexity, symmetry, z score; MI: myocardial infarction; n: number of patients with (at least one) event; N: number of analysed patients in the relevant subpopulation; ND: no data; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 5: Results (continuous outcomes) – COMBO II: alirocumab + statin vs. ezetimibe + statin

Study **Outcome category**	**Alirocumab + statin**			**Ezetimibe + statin**			**Alirocumab vs. ezetimibe**
Time point Outcome	**N[a]**	**Baseline values mean (SD)**	**Change at end of study mean[b] (SE)**	**N[a]**	**Baseline values mean (SD)**	**Change at end of study mean[b] (SE)**	**MD [95% CI]; p-value**
COMBO II							
Supplementary outcome							
Results after week 104: The company did not present results after week 104							
Results after week 52:							
LDL-C (mg/dL)	171	99.8 (29.8)	−51.3 (2.9)	86	102.6 (31.3)	−12.1 (4.0)	−39.2 [−48.4; −29.9]; < 0.001[c]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study (if applicable at other time points) may be based on other patient numbers.
b: MMRM analysis of the ITT population.
c: Institute's calculation from data on the 95% CI.
CI: confidence interval; ITT: intention to treat; LDL: low-density lipoprotein; LDL-C: LDL cholesterol; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients in the relevant subpopulation; SD: standard deviation; SE: standard error; vs.: versus

Mortality

All-cause mortality

No data at the time point 104 weeks were available for the outcome "all-cause mortality".

One death had occurred in each of the 2 treatment groups after 52 weeks. The result was not statistically significant. Overall, this resulted in no hint of an added benefit of alirocumab for the outcome "all-cause mortality"; an added benefit is not proven for this outcome.

Morbidity

Cardiovascular events

Cardiovascular events were recorded in the framework of the recording of adverse events (AEs) and assessed by an adjudication committee.

No data at the time point 104 weeks were available for the outcome "cardiovascular events".

A cardiovascular event had occurred in about 5% of the patients in both treatment groups after 52 weeks. The result was not statistically significant. The results for individual events (myocardial infarction, stroke, etc.) were also not statistically significant in each case. Overall, this resulted in no hint of an added benefit of alirocumab for the outcome "cardiovascular events"; an added benefit is not proven for this outcome.

Health-related quality of life

No relevant data were available for the outcome "health-related quality of life" after 52 weeks or after 104 weeks. Overall, this resulted in no hint of an added benefit of alirocumab for the outcome "health-related quality of life"; an added benefit is not proven for this outcome.

Side effects

No data were available for side effects for the observation period after 104 weeks.

After 52 weeks, a serious adverse event (SAE) had occurred in about 20% of the patients in both treatment groups; about 8% of the patients discontinued treatment due to an AE. The result for both outcomes was not statistically significant.

The company only presented incomplete analyses on specific AEs for the relevant subpopulation, namely only for predefined AEs of particular interest. A numerically notable difference between the treatment groups was only shown for general allergic reactions and allergic injection site reactions. The number of these events was higher under alirocumab, but the result was not statistically significant. However, it should be pointed out that the risk of such events was probably overestimated because of the double blinding and the resulting necessity of placebo injections in the comparator arm.

In the overall consideration, there was no hint of greater or lesser harm from alirocumab for AE-related outcomes; an added benefit for these outcomes is therefore not proven.

2.4 Summary

The following Table 6 shows an overview of the positive and negative effects resulting from the COMBO II study for alirocumab in combination with a statin in comparison with ezetimibe plus statin for patient-relevant outcomes.

Table 6: Positive and negative effects for alirocumab + statin vs. ezetimibe + statin – study COMBO II

Positive effects	**Negative effects**
Results after week 104: Results after week 104 were not presented	
Results after week 52: no positive or negative effects	

In the overall consideration, neither positive nor negative effects of alirocumab in comparison with ezetimibe on patient-relevant outcomes were determined after week 52. The company did not present the results after week 104.

Hence in summary, there is no proof of an added benefit of alirocumab in comparison with the ACT for research question A (patients for whom statins are a treatment option). The assessment of dossier assessment A15-47 was therefore not changed by the data subsequently submitted by the company for research question A.

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

3.1 Analyses subsequently submitted

In its dossier, the company presented no study on research question C. The ESCAPE study was not yet completed at the time of submission of the dossier. Subsequent to its written comments, the company presented an analysis of the ESCAPE study in the form of a "key note report" [5] supplemented with individual analyses on patients from Germany [6] and processing of the data on the basis of the dossier templates [7]. The study protocol on the ESCAPE study was already contained in the original dossier [12].

3.2 Assessment of the ESCAPE study

The ESCAPE study was a double-blind multicentre RCT conducted in the USA and Germany (proportion about 50% each). Patients with heterozygous hypercholesterolaemia currently undergoing low-density lipoprotein (LDL) apheresis therapy (weekly or every 2 weeks) and, if applicable, additional lipid-lowering treatment were included. The aim of the study was to evaluate the effect of alirocumab on the frequency of necessary LDL apheresis treatments. In addition, the effect of alirocumab (or of the anticipated reduction in LDL apheresis frequency) on health-related quality of life was investigated. AEs, SAEs, discontinuations due to AEs, and several laboratory parameters (including the LDL-C) were also recorded in the course of the study.

Patients were allocated in a ratio of 2:1 to treatment with alirocumab or placebo. In the first 6 weeks of the study, the ongoing treatment including LDL apheresis was maintained stable. In the following 12 weeks, LDL apheresis treatment was conducted depending on the current LDL-C value. The patients were observed over a period of 18 weeks in total.

No added benefit of alirocumab in comparison with the appropriate comparator therapy could be derived from the ESCAPE study for several reasons:

1) The criterion used in the ESCAPE study for not conducting LDL apheresis was unsuitable. Directly before the planned LDL apheresis date, the LDL-C value was determined to assess the necessity of LDL apheresis. If this value was at least 30% below the baseline LDL-C value, no LDL apheresis was conducted. This relative lowering allowed no conclusion on whether the individual target LDL-C level was reached, however. In a concrete example of a baseline LDL-C value of 200 mg/dL, a 30% lowering was already reached with an LDL-C value of 140 mg/dL. This value is notably above the LDL treatment goals mentioned by the company in the dossier (the company described a target level of 70 mg/dL for the present patient population). On the one hand, this resulted in an underestimation of the frequency of necessary LDL aphereses in the alirocumab arm. On the other, the treatment in the alirocumab arm did not concur with the common approach, also making the results for other outcomes (AEs, health-related quality of life) unusable. This particularly applies to the specific outcome "LDL-C value too low

(< 25 mg/dL) and subsequently occurring AEs", which was recorded separately in the ESCAPE study.

2) It was not ensured that the patients included in the study had received their individual maximum lipid-lowering treatment. As in the COMBO II study (see dossier assessment A15-47 [1] and Chapter 2), there was a broad spectrum of reasons for a non-maximum statin dose. Up to 23% of the patients in the ESCAPE study did not fulfil the operationalization chosen by the company for the COMBO II study for the categorization of the subpopulation relevant for research question 2 (see Chapter 2). Other lipid-modifying drugs (including ezetimibe) were only used in about 67% of the patients. As a consequence, LDL apheresis was therefore either 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 again because the aim of the ESCAPE study was to evaluate the potential for reducing LDL apheresis treatments by escalating drug treatment, and for a fair comparison this would have been meaningful and necessary also in the comparator arm.
   In contrast to the analysis for the COMBO II study, the company presented no separate analysis of patients in whom individual maximum lipid-lowering treatment could be assumed for the ESCAPE study.

3) The ESCAPE study had a treatment and observation period of 18 weeks and was therefore too short to draw conclusions on long-term treatment with alirocumab. Irrespective of the missing suitability of the criterion for not conducting LDL apheresis mentioned above, it can particularly not be derived from a study with such a short duration that LDL aphereses are not necessary in the long term under use of alirocumab.

4) Irrespective of the question whether the outcome "number of LDL aphereses" per se is patient-relevant, the ESCAPE study showed no advantage regarding health-related quality of life measured with the Well-Being Questionnaire with 22 items (W-BQ22). The difference between the treatment groups (difference in comparison with baseline) was 2.35 points (95% confidence interval [−1.19; 5.88]; p = 0.189). In the oral hearing on alirocumab, the company argued that the scale used might not have been sufficiently sensitive so that no advantage of alirocumab was determined despite notable reduction in apheresis frequency[3]. The company itself justified the use of the W-BQ22 scale in the study protocol of the ESCAPE study by claiming that an advantage over apheresis treatment had been determined for another drug treatment (statins) [12]. Hence the W-BQ22 scale is apparently principally sufficiently sensitive for revealing relevant differences in the present treatment context. Irrespective of the scale used, the ESCAPE study was too short also for the assessment of the effects of long-term alirocumab treatment on health-related quality of life.

[3] In comparison with the apheresis frequency at baseline, the frequency between week 7 and week 18 was about 13% in the alirocumab group, and about 81% in the placebo group (p-value for median difference: p < 0.001).

3.3 Summary

In summary, no proof of an added benefit of alirocumab in comparison with the appropriate comparator therapy resulted from the ESCAPE study for research question C (patients in whom drug and dietary options to reduce lipid levels have been exhausted). The assessment of dossier assessment A15-47 was therefore not changed by the data subsequently submitted by the company for research question C.

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